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ANTIBIOTIC COMBINATIONS*

Antistreptococcal and Antistaphylococcal Activity of Plasma of Normal Subjects after Ingestion of Erythromycin or Penicillin or Both

WILFRED F. JONES, JR., M.D.,† AND MAXWELL FINLAND, M.D.‡

With the Technical Assistance of Clare Wilcox and Ann Najarian

BOSTON

JAWETZ and his co-workers[1] have presented evidence that certain combinations of antibiotics may be less effective in their antibacterial action than comparable amounts of the same agents acting separately. Such "antagonisms" have been demonstrated in vitro and in some experimental infections, mostly in mice, but, except for the report of Lepper and Dowling[2] on the possible antagonistic action of chlortetracycline and penicillin in the treatment of pneumococcal meningitis, there has been little or no reliable clinical evidence for such an antagonistic action among antibiotics. Moreover, such evidence is difficult to obtain because of the many problems involved in conducting adequately controlled clinical therapeutic studies.

Since the clinical effectiveness of antibiotics in the treatment of infections is dependent, in the first instance, on their antibacterial action against the causative micro-organisms, it seemed worth while to explore the possibility of approaching the subject of antibiotic synergisms and antagonisms directly in human beings by comparing the antibacterial property of the blood after administration of antibiotics singly and in combinations. Because Coleman, Gunnison and Jawetz[3] reported evidence of antagonism in vitro between erythromycin and penicillin, this combination seemed to be a good one to explore. This paper presents the results of studies of the antistreptococcal and antistaphylococcal action of plasma after administration of various preparations of erythromycin, penicillin and combinations of these antibiotics to the same subjects.

*From the Thorndike Memorial Laboratory, Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

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†Assistant in medicine, Harvard Medical School; research fellow, Thorndike Memorial Laboratory.

‡Associate professor of medicine, Harvard Medical School; associate director, Thorndike Memorial Laboratory, and physician-in-chief, Fourth Medical Service, Boston City Hospital.

MATERIALS AND METHODS

The subjects were normal young men who ranged in age from twenty-four to thirty-five years and in weight from 64 to 86 (average, 78) kg. This study was conducted in the same manner as earlier ones in which different preparations of penicillin were compared.[4,5] Each subject received a dose of one of the test antibiotics or combinations half an hour before breakfast, and venous blood was drawn immediately before and at stated intervals after the dose. The plasma was removed promptly and stored at −20°C. until the time of the assays. All the test agents under comparison were given to different subjects on each day, and each subject received, in rotation, all the antibiotic preparations that were being studied. At least three days elapsed between the successive experiments in which the different antibiotics were given to all the subjects. Each subject, therefore, acted as his own control, and all the bloods collected on the same day were tested simultaneously, to minimize the effect of variations in the conditions of the assays.

Two separate studies were conducted. In the first, a combination of 250 mg. of erythromycin and 125 mg. of penicillin was provided in a single capsule,§ and a dose of 1 capsule (EV_c) was compared with the following: first, 375 mg. of penicillin V given as 3 tablets of 125 mg. each (V); secondly, 375 mg. of a suspension of erythromycin ethyl carbonate (E_s); and, thirdly, 250 mg. of the latter suspension plus a 125-mg. tablet of penicillin V (E_sV). In the second experiment the combination of erythromycin and penicillin G was compared with its individual com-

§All the preparations of erythromycin (Ilotycin), including the capsules containing both erythromycin and penicillin V, were provided by Eli Lilly and Company, Indianapolis, Indiana, through the courtesy of Dr. R. S. Griffith; the tablets of penicillin V (*Pen Vee*, oral) were supplied by Wyeth Laboratories, Philadelphia, through the courtesy of Dr. Edward F. Roberts and tablets of buffered potassium penicillin G were provided by E. R. Squibb and Sons, New York City.

ponents, each subject receiving, in rotation, one of the following: 500 mg. (4 tablets) of buffered potassium penicillin G (G); 500 mg. of the suspension of erythromycin ethyl carbonate (E_s); 500 mg. of erythromycin as 2 "specially coated" tablets (E_t); and 1 250-mg. tablet of erythromycin plus 250 mg. (2 tablets) of buffered potassium penicillin G (E_t+G).

TABLE 1. *Comparative Efficacy of Various Antibiotics in Inhibiting Test Strains.*

ANTIBIOTIC	NO. OF 2-FOLD DILUTIONS* OF 1 MICROM. INHIBITING TEST STRAINS	
	STR. 98	STAPH. 209P
Erythromycin (E)	6	3
Penicillin V (V)	6½	6
Penicillin G (G)	6½	5
2 parts E+1 part V	6	4½
E+G (=parts)	6½	4½

*±½ in control tests of these strains done in present experiments.

Assays of the antibacterial action of plasma were carried out as in the previous studies.[5] Twofold dilutions of plasma were made in brain-heart infusion broth (Difco, pH 7.4±) and each specimen was tested with 2 standard assay organisms, *Streptococcus 98* and *Staphylococcus 209P*,* which have been employed in other studies in this laboratory[5]; 0.5 ml. of a 10^{-4} dilution of an overnight growth of the organism was added to an equal volume of the dilutions of plasma. The tubes were examined for growth after incubation for eighteen hours at 37°C. The antibiotic activity of each specimen of plasma was expressed as the maximum dilution of the plasma that yielded no growth. When there was marked but incomplete inhibition† in the dilution beyond that which gave no growth, the value of the end point was arbitrarily taken to be one-half dilution greater. In the text figures, these values are charted, for convenience, as the reciprocals of these dilutions. Also, for convenience in calculating average values, the arithmetic means of the number of twofold dilutions that produced inhibition of the test strains were arbitrarily chosen for comparisons. These were also used to compare the total antibacterial activity in the plasma derived from any given dose; this activity was expressed in "dilution hours" to approximate the areas subtended under the curves representing the levels of antibacterial activity.[5] For these areas, one hour was taken as the unit of time, and one twofold dilution of plasma as representing 1 "unit" of activity, the unit "area" thus representing one dilution hour. When the last specimen still exhibited some inhibitory activity, the area beyond that time was estimated by extrapolation from the slope of the curve of the plasma levels, but all the areas were calculated only for the period of sixteen hours after the dose.

The values for blood levels were not expressed in units or micrograms because of the difficulties in making comparisons on this basis. However, these values can be calculated by comparisons of the number of twofold dilutions of broth containing 1 microgm. per milliliter of each of the antibiotics that inhibited the test strains (Table 1).

Staph. 209P was obtained from Dr. Donald S. Grove, Division of Antibiotics, Food and Drug Administration.

†As evidenced by slight, but barely discernible growth or by incomplete hemolysis of the red blood cells used in the medium as an indicator.

RESULTS

The results of the assays done with *Str. 98* on the plasmas of the subjects who participated in the first experiment on the comparison of 375-mg. doses of

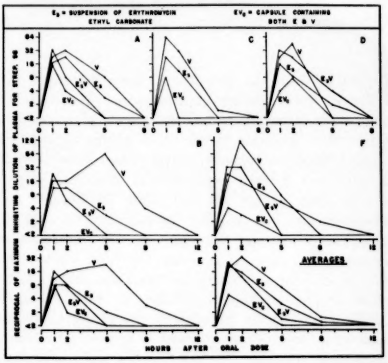

FIGURE 1. *Inhibiting Levels for* Str. 98 *in Plasma of 6 Subjects after Ingestion of 375 Mg. of Erythromycin (E) or Penicillin V (V) or a Mixture of Two Parts E and One Part V.*

erythromycin and penicillin V, separately and in combinations, are shown graphically in Figure 1. The curves representing the inhibitory activity of the plasmas from each subject with all the dosage forms are shown together in individual panels, and the average values obtained in all the subjects for all the dosage forms are also shown (in the lower right panel).

The results were more or less uniform, at least in the relative activity of the plasma resulting from the different antibiotics and combinations. Peak values were achieved in almost every assay in one or two hours. These peak values appeared to be highest, and the levels were sustained best with penicillin V; the peaks were lowest, and insignificant levels were reached soonest when the capsule containing erythromycin and penicillin V was taken. The peak values for the suspension of erythromycin ethyl carbonate or the combination of this suspension with penicillin V varied, ranking either second or third in the different subjects. The average values for these levels

reflect the same relations, except that those for the erythromycin suspension appear to be somewhat better sustained than those for its combination with penicillin V; the average peak values, however, appear to be quite similar.

The corresponding tests done on the same bloods with *Staph. 209P* are depicted in Figure 2. They show almost identical relations, but the lesser susceptibility of the staphylococcus to these agents, as compared with that of the streptococcus, is reflected in the lower levels of inhibitory activity that were almost regularly found in the same samples of plasma.

The average peak values and the average total inhibitory activity obtained from each of the dosage forms in this experiment, as represented in the estimated dilution hours, are given in Table 2, together with a representation of the statistical significance of the differences of these means ("P" values). From this table it is seen that the differences between the peak levels obtained with penicillin V as compared with those from the erythromycin suspension and from the capsule containing erythromycin and penicillin V are significant in each instance ($P \leq 0.05$),

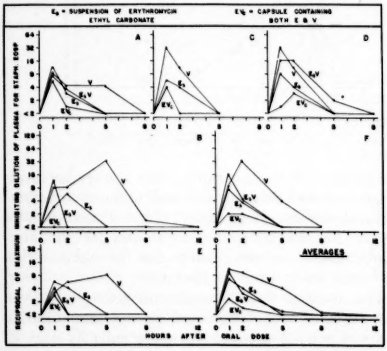

FIGURE 2. *Inhibiting Levels for* Staph. 209P *in Plasma of 6 Subjects after Ingestion of 375 Mg. of Erythromycin (E) or Penicillin V (V) or a Mixture of Two Parts E and One Part V.*

but the difference between the average peak levels from penicillin V and from its combination with the suspension of erythromycin ethyl carbonate is not significant. Likewise, the average peak level of activity from the erythromycin suspension is significantly higher than that obtained with the combination in the capsule, but is not significantly different from the average peak level produced by the combination of the erythromycin suspension and the tablet of penicillin V. Regarding the two combinations used, the average peak level for the one employing the suspension was significantly higher than that contained in the capsule.

The significance of these differences was similar in every instance for the tests employing the streptococcus and for those assayed with the staphylococcus.

The values estimated to represent the total inhibitory activity resulting from the different dosages used are also given in Table 2. It is seen that this activity, calculated as the average of the areas under the curves of the maximum inhibitory concentrations

TABLE 2. *Average Values for the Inhibition of Two Test Strains by Plasma after Ingestion of 375 Mg. of Erythromycin (E) or Penicillin V (V) or a Combination of Two Parts E and One Part V.*

ANTIBIOTIC*	NO. OF SUBJECTS	AVERAGE MAXIMUM INHIBITING DILUTION OF PLASMA ± SD†		AVERAGE "AREAS" ± SD (DILUTION HOURS)‡	
		STR. 98	STAPH. 209P	STR. 98	STAPH. 209P
V	6	5.7±0.85	4.3±1.0	25.0±7.6	16.2±5.8
E_sV	5	4.5±0.87	3.3±0.83	12.9±4.7	7.1±5.0
E_s	6	4.4±0.67	2.8±0.42	17.6±5.3	6.7±0.29
EV_c	6	2.5±1.4	1.4±0.86	4.8±3.1	2.2±1.4
Significance of differences of means ("P" values):					
V-E_sV		>0.05	>0.1	0.02	<0.05
V-E_s		<0.05	<0.02	0.1	<0.01
V-EV_c		<0.01	<0.001	<0.001	<0.001
E_s-E_sV		>0.1	>0.1	>0.1	>0.1
E_s-EV_c		0.02	<0.01	0.001	<0.001
E_sV-EV_c		<0.05	<0.01	<0.02	>0.05

*E_s = suspension of erythromycin ethyl carbonate; EV_c = capsule containing E + V.

†Expressed as mean of maximum number of 2-fold dilutions of serum that inhibited test strain.

‡Calculated as in previous study by Jones and Finland.[5]

of the plasma, was highest for penicillin V and lowest for the capsule in which one part of this antibiotic was combined with two parts of erythromycin; this was equally true for the tests with both organisms. The antistreptococcal activity of the suspension of erythromycin ethyl carbonate ranked above the combination in which it was used with penicillin V, but the average value for the antistaphylococcal activity was slightly higher for the combination.

The significance of the differences of the average values of these "areas" is also given. The difference between the total activity derived from penicillin V and that resulting from each of its two combinations with erythromycin was significant in each instance. The average area representing the total activity derived from the suspension of erythromycin ethyl carbonate was not significantly different from those obtained from penicillin V or from the combination of these 2, but the mean values for these areas calculated for both of the preparations containing the erythromycin suspension were significantly greater than those derived from the combination contained in the capsule. In all assays the significance of these differences was similar for the tests done with *Staph.*

209P and *Str. 98*, except that, whereas penicillin V produced a significantly greater total area of antistaphylococcal activity than the erythromycin suspension, the difference of the total antistreptococcal activity of these two antibiotics was not significant.

Differences in absorption of erythromycin tablets, depending on the nature of the coating used, have previously been demonstrated by Griffith[6] and by Kirby et al.[7] It was therefore of interest to compare the absorption of one type of tablet of erythromycin currently being manufactured with that of the suspension of erythromycin ethyl carbonate. It was also of interest to determine whether any apparent antagonism, similar to that observed for the combination of erythromycin and penicillin V in the capsule, would also become apparent for combinations of both these forms of erythromycin (the tablet and the suspension) with penicillin G, the latter being given in its most commonly used oral form — namely, the tablets of buffered potassium penicillin G. The second experiment was therefore designed with these objectives in view.

The results of the second experiment are shown in Figures 3 and 4 for the tests done with *Str. 98* and *Staph. 209P*, respectively. The individual levels and the means for each of the dosage forms used are shown in separate panels, and the average values are also shown together in the lower right panels. For each of the dosage forms, the absorption was similar in the different subjects, as indicated by the close similarity of the curves of the levels of activity in the plasma, which are, therefore, not drawn in. However, absorption of the erythromycin tablets was very irregular in the different subjects, as shown by the curves in the upper right panels of Figures 3 and 4. An irregular absorption curve, probably representing successive absorption of penicillin G and of the erythromycin tablets, was exhibited by one of the subjects, and the curve of his plasma levels has been drawn in and is shown in the upper middle panel of Figure 3; this was clearly observed in this subject only in the tests employing *Str. 98*.

From Figures 3 and 4 it is also seen that the curves representing the average values for the inhibitory activity are similar for all the preparations, except for the lower peak levels obtained with the erythromycin suspension and the irregular absorption of the erythromycin tablets. Here, again, the findings are very similar for the antistreptococcal and for the antistaphylococcal activity, except for the more or less uniformly lower levels of the latter.

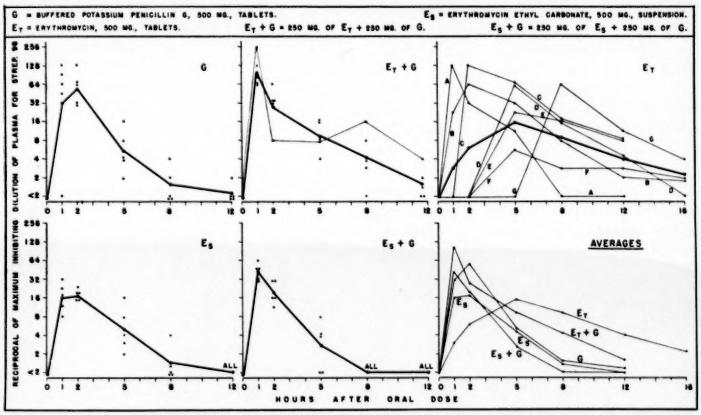
G = BUFFERED POTASSIUM PENICILLIN G, 500 MG., TABLETS.
E_T = ERYTHROMYCIN, 500 MG., TABLETS.
E_T + G = 250 MG. OF E_T + 250 MG. OF G.
E_S = ERYTHROMYCIN ETHYL CARBONATE, 500 MG., SUSPENSION.
E_S + G = 250 MG. OF E_S + 250 MG. OF G.
RECIPROCAL OF MAXIMUM INHIBITING DILUTION OF PLASMA FOR STREP. 98
G
E_T + G
E_T
E_S
E_S + G
AVERAGES
ALL
HOURS AFTER ORAL DOSE

FIGURE 3. *Inhibition of* Str. 98 *by Plasma after Ingestion of Erythromycin or Penicillin or Both.*

The averages for the maximum activity achieved and for the "areas" representing the total dilution hours of activity produced in the plasma by each of the dosage forms are shown in Table 3. Estimates of the statistical significance of the differences of these mean values are also shown. These data indicate that the peak levels of antistreptococcal activity achieved with the erythromycin tablets are not significantly different from those obtained from any of the other dosage forms. The tablets of penicillin G produced significantly higher average peak levels than the erythromycin suspension when used either alone or in combination with penicillin, but not significantly different from its combination with the erythromycin tablet. Both the combinations of erythromycin with penicillin gave significantly higher average peak levels of activity than was obtained with the erythromycin suspension. The significance of all these differences was similar in the tests done

with the staphylococcus except that there was no significant difference between, on the one hand, the average of the peak levels resulting from ingestion of the two combinations of erythromycin and penicillin G and, on the other, the average obtained with penicillin G alone and in its combination with the erythromycin suspension.

Regarding the average values for the number of dilution hours of antistreptococcal activity produced by the different forms, there was no significant difference between the tablets of erythromycin and ingestion of the various preparations, however, was the same in the tests done with staphylococcus as in those done with the streptococcus, with one exception. Whereas against *Str. 98* the average number of dilution hours of activity produced by the erythromycin suspension was greater than that resulting from its administration in combination with penicillin G, the reverse was true when *Staph. 209P* was used for the assays. The significance of the differences between the total numbers of dilution hours of antibacterial activity produced by any pair of the

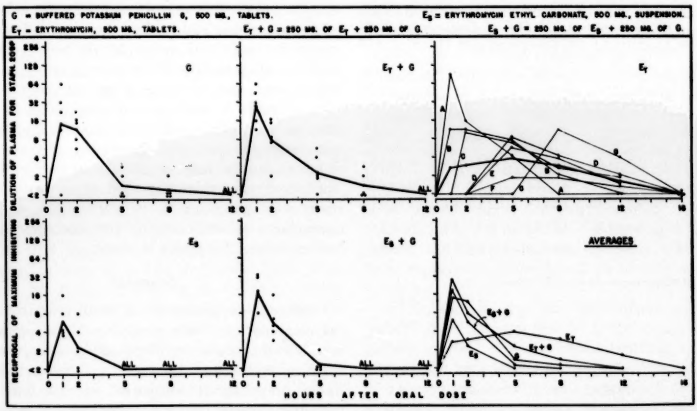
G = BUFFERED POTASSIUM PENICILLIN G, 500 MG., TABLETS.
E_T = ERYTHROMYCIN, 500 MG., TABLETS.
E_T + G = 250 MG. OF E_T + 250 MG. OF G.
E_S = ERYTHROMYCIN ETHYL CARBONATE, 500 MG., SUSPENSION.
E_S + G = 250 MG. OF E_S + 250 MG. OF G.
RECIPROCAL OF MAXIMUM INHIBITING DILUTION OF PLASMA FOR STAPH. 209P
AVERAGES
HOURS AFTER ORAL DOSE

FIGURE 4. *Inhibition of* Staph. 209P *by Plasma after Ingestion of Erythromycin or Penicillin or Both.*

those of penicillin G or between the former and the combination of the two tablets (erythromycin and penicillin G). However, the number of dilution hours of activity derived from the erythromycin tablets was significantly greater than that from the erythromycin suspension, used either alone or in combination with penicillin G. Penicillin G alone was not significantly different, in this regard, from any of the four other dosage forms tested. The average number of dilution hours of activity produced by the erythromycin suspension was significantly less than that from the combination of the erythromycin tablet with penicillin G but was not significantly different from the combination of the latter with the erythromycin suspension. Of the two combinations of erythromycin with penicillin G the one in which the specially coated tablet was employed provided significantly greater average total activity than the one with the suspension.

As in the first experiment and also with the peak levels in this experiment, all the values for the activity of the plasmas were much lower for the tests done with the staphylococcus. The relative order of the total antistaphylococcal activity resulting from dosage forms, however, was similar for the tests done with each of the assay organisms. There was only one exception: penicillin G yielded a significantly greater average total amount of activity than that resulting from the ingestion of the suspension of erythromycin ethyl carbonate.

Discussion

The results in the first experiment seemed to suggest some antagonism between erythromycin and penicillin V when they were used together in a ratio of two parts erythromycin and one part penicillin V. The capsule containing a total of 375 mg. of this combination produced significantly lower peak concentrations and smaller total amounts of antibacterial action than was yielded by the same number of milligrams of either penicillin V alone or of erythromycin alone. However, some doubt was entertained regarding the interpretation of these differences as representing antagonism, for the possibility had to be considered that the difference was related in some way to the dosage formulation used — either to the type of capsule used, to some direct interaction of the erythromycin with the penicillin V as they were re-

leased from the capsule or to some other factors related to their absorption rather than to their interaction.

The possibility that some such factors were involved was also suggested by the fact that there was no significant difference between the antibacterial activity resulting from the suspension of erythromycin ethyl carbonate and that derived from the combination of that suspension with penicillin V. However, the latter combination, although yielding similar peak levels of activity as the same amount of penicillin V, gave less sustained levels and hence a significantly lower total activity, as indicated by the smaller number of dilution hours.

TABLE 3. *Average Values for Inhibition of Two Test Strains by Plasma after Ingestion of 500 Mg. of Erythromycin (E) or Penicillin G (G) or Combinations of 250 Mg. of E and 250 Mg. of G.*

Antibiotic*	No. of Subjects	Average Maximum Inhibiting Dilution of Plasma ± SD†		Average "Areas" ± SD (Dilution Hours)‡	
		STR. 98	STAPH. 209P	STR. 98	STAPH. 209P
E_t	7	5.6±1.6	3.4±1.6	39.5±13.0	18.9±5.5
E_tG	5	6.7±0.78	4.8±1.1	35.8± 9.6	16.2±4.7
G	5	6.5±0.49	4.5±1.3	26.8± 6.4	13.2±2.1
E_sG	5	5.4±0.35	4.2±0.87	18.2± 5.2	9.8±3.0
E_s	5	4.3±0.43	2.6±0.87	21.0± 5.6	5.0±3.4
Significance of differences of means ("P" values):					
E_t-E_tG		>0.1	>0.1	>0.1	>0.1
E_t-G		>0.1	>0.1	0.1	>0.05
E_t-E_sG		>0.1	>0.1	0.01	<0.02
E_t-E_s		>0.1	>0.1	<0.02	0.001
G-E_sG		<0.01	>0.1	>0.05	0.1
G-E_s		<0.001	<0.05	>0.1	<0.01
G-E_tG		>0.1	>0.1	>0.1	>0.1
E_s-E_tG		<0.001	<0.02	<0.05	<0.01
E_s-E_sG		<0.01	<0.05	>0.1	>0.05
E_tG-E_sG		<0.02	>0.1	<0.02	0.05

*E_t = coated tablet of erythromycin; E_s = suspension of erythromycin ethyl carbonate.

†Expressed as mean of maximum number of 2-fold dilutions of serum that inhibited test strain.

‡Calculated as in previous study by Jones and Finland.[5]

These findings, and the possibility that the combination of penicillin V and erythromycin was not a satisfactory one because penicillin V is absorbed well, even after it is exposed to the acidity of the stomach, whereas erythromycin is absorbed much better from an alkaline medium,[7] prompted the use of the combination of penicillin V with the erythromycin ethyl carbonate in the first experiment. These considerations also prompted the use of the buffered potassium penicillin G and both the erythromycin ethyl carbonate and the "specially coated" tablets of erythromycin for comparisons when used separately and in combinations, since presumably the effects of exposure to the acidity of the stomach would thus be averted — at least, to some extent.

The tests with these forms showed mainly that the erythromycin suspension was either poorly absorbed or inactivated, since both the peak levels of activity and the total antistaphylococcal activity it produced were less than those resulting from penicillin G, whereas the tablets containing the same amount of erythromycin produced peak levels and total activity in the plasma that were comparable to those induced by similar amounts of penicillin G.

These findings and some of the other comparisons suggest that there was no definite evidence of antagonism, but rather that the observed differences could be explained better by the relatively greater activity of penicillin V as compared with erythromycin and also by some local interaction between the penicillin V and erythromycin, either in the capsule or after their release from the capsule. They also suggest that the suspension of erythromycin ethyl carbonate may be inferior to the erythromycin tablet, whether these are used alone or in combinations with penicillin G, in spite of the much more irregular manner in which the erythromycin is absorbed when the tablet is given.

Summary

Different preparations of erythromycin, alone or in combinations with penicillin V or penicillin G, and also the two forms of penicillin alone, were given in comparable total amounts, and the activity of all these preparations compared on the basis of the antistreptococcal and antistaphylococcal activity that they produced in the plasma of normal subjects. Many differences were revealed, some of which suggested the possibility that erythromycin and penicillin V were manifesting antagonistic action. Further study of the data, however, revealed differences in the absorption of the various dosage forms that, together with previously demonstrated differences in activity of oral preparations of penicillins V and G, might be responsible for most of the difference in activity observed when all these agents were used singly or in combinations of erythromycin with penicillin.

References

1. Jawetz, E., and Gunnison, J. B. Experimental basis of combined antibiotic action. *J.A.M.A.* **150**:693-695, 1952.
2. Lepper, M. H., and Dowling, H. F. Treatment of pneumococcic meningitis with penicillin compared with penicillin plus Aureomycin: studies including observations on apparent antagonism between penicillin and Aureomycin. *Arch. Int. Med.* **88**:489-494, 1951.
3. Coleman, V. R., Gunnison, J. B., and Jawetz, E. Participation of erythromycin and carbomycin in combined antibiotic action *in vitro*. *Proc. Soc. Exper. Biol. & Med.* **83**:668-670, 1953.
4. Wright, S. S., Purcell, E. M., Kass, E. H., and Finland, M. Penicillin G and Benzethacil by mouth: comparison of penicillin levels in plasma of normal men after single oral doses. *J. Lab. & Clin. Med.* **42**:417-429, 1953.
5. Jones, W. F., Jr., and Finland, M. Blood levels from orally administered penicillins G and V: relation to food intake. *New Eng. J. Med.* **253**:754-761, 1955.
6. Griffith, R. S. Blood levels and clinical results with erythromycin. In *Antibiotics Annual 1954-1955: Proceedings of the second annual symposium on antibiotics.* Edited by H. Welch and F. Marti-Ibañez. 1154 pp. New York: Medical Encyclopedia, 1955. Pp. 269-278.
7. Kirby, W. M. M., Maple, F. M., and O'Leary, B. Erythromycin serum concentrations following administration in acid-resistant tablets. *Antibiotics & Chemother.* **3**:473-477, 1955.

STUDIES IN REGIONAL HEPARINIZATION*

I. The Use of Simultaneous Neutralization with Protamine — Preliminary Studies

LEON A. GORDON, M.D.,† VICTOR RICHARDS, M.D.,‡ AND HERBERT A. PERKINS, M.D.§

SAN FRANCISCO

REGIONAL heparinization is a technic whereby heparin is infused into an artery at such a rate that the coagulation time of the blood is prolonged in the area supplied by that artery, but the clotting time in the rest of the body remains normal owing to dilution of the heparinized blood. The technic has been applied primarily after operations on an artery, such as endarteriectomy, in which there is a considerable possibility that postoperative thrombosis will result in obstruction of the vessel. This danger is particularly great when the distal arterial bed is partially obstructed by atherosclerosis. A number of reports indicate that it is possible to infuse heparin regionally in this manner,[1,2] but experience has shown that it does not always prevent thrombus formation. The most obvious explanation for this is that the level of heparin in the involved vessel must be kept very low if general heparinization is to be avoided. The recommended clotting time of fifteen to twenty minutes in the heparinized area is hardly out of the normal range. On the other hand, if heparin is infused rapidly enough for prophylaxis of thrombosis, general heparinization occurs, and there is no advantage to administering the anticoagulant in the involved artery; it might just as well be given by intravenous infusion into an easily accessible surface vein.

Systemic heparinization for the control of this problem also has its disadvantages. In the doses usually given, postoperative thrombosis is common. From a theoretical point of view it should be possible to prevent this clotting. Regardless of stasis and the local accumulation of thromboplastin or thrombin, or both, clotting should be avoidable if a sufficiently high level of heparin can be attained. Heparin can neutralize thrombin and thromboplastin if present in high enough concentration[3-7] and can also prevent the formation of platelet thrombi.[8] Understandably, however, there has been reluctance to use doses that prolong the clotting time more than two or three times. A number of reports attest to the fact that the use of heparin may be associated with massive bleeding.[9-11] However, no evidence has been presented that the anticoagulant will *initiate* bleeding or that higher levels are more likely to be associated with bleeding than those customarily attained. This is in contrast to the coumarin anticoagulants, which are associated with bleeding very commonly when their effect goes beyond the usual therapeutic range. Although one study[12] suggests a damaging effect of heparin on blood vessels the reported cases of hemorrhage from this cause suggest an underlying pathologic lesion that initiated bleeding, which, in the presence of heparin, became profuse. Recent experiences with heart operations using a mechanical heart-lung apparatus prove that, if severed vessels are carefully tied, there will be no unusual bleeding during the operation even though high concentrations of heparin are used (2.5 mg. per kilogram of body weight).[13] Nonetheless, the fact that severe bleeding episodes have been reported in heparinized patients is a cause for caution.

A technic of regional heparinization that will permit high enough levels to prevent thrombosis locally but will retain a normal clotting time in the rest of the circulation would overcome the difficulties mentioned above. The experience of one of us (H.A.P.) with the use of protamine to neutralize heparin after operations with an artifical heart-lung machine suggested a means of accomplishing this. We have used a simplified protamine titration method[14] that permits rapid determination of the minimal amount of a given lot of protamine that will neutralize the heparin in an animal or patient.

Our aims in this study were to find out, first, whether it would be possible to infuse large amounts of heparin into a regional artery and to neutralize it in the corresponding vein with a simultaneous infusion of protamine, controlling the rates of flow of the two solutions with our protamine titration test. A second question was whether the large amounts of heparin and protamine infused, even though largely combined into an inactive complex, would prove toxic.

MATERIALS AND METHODS

Adult mongrel dogs weighing between 5 and 22 kg. were used. They were anesthetized with intravenous infusions of pentobarbital sodium. Heparin¶ was infused into one femoral artery, and protamine‖

*From the departments of Surgery and Medicine, Stanford University School of Medicine.
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†Resident in surgery, Monterey County Hospital, Salinas, California; formerly, assistant resident in surgery, Stanford University Hospitals.

‡Executive and professor of surgery, Stanford University School of Medicine.

§Clinical instructor in medicine, Stanford University School of Medicine.

¶Kindly supplied as Upjohn heparin sodium, 10 mg. per milliliter, by the Upjohn Company, Kalamazoo, Michigan.

‖Kindly supplied as Lilly 1 per cent solution by Eli Lilly and Company, Indianapolis, Indiana.

into the corresponding femoral vein. Various quantities of each, as indicated below under Results, were diluted by addition to 250-ml. bottles of isotonic saline solution. The ratios of the concentrations of the heparin and protamine solutions were adjusted so that at a constant and equal rate of flow protamine would be added at the correct rate to neutralize the infused heparin. Each infusion bottle was attached to a sterile, disposable set for intravenous administration.

It was found impossible to rely on gravity to provide a constant equal flow from the two bottles because of the marked difference in pressure between the femoral artery and vein; some kind of constant-infusion pump was required. One of us (L.A.G.) devised a method that made use of a single Sigmamotor pump,* which is known to deliver relatively constant volumes for prolonged periods against widely different resistances. Since the pump is adapted to compress a wide-bore rubber tube and since our experiments required slow rates of flow, the method provided a means of inserting two fine-caliber tubes simultaneously into the slot of the pump. Two matched No. 12 French rubber catheters were laid in parallel through a section of gum-rubber tubing. The catheters were secured to the outside tubing with adhesive tape. The entire assembly was inserted into the pump. It could be cold sterilized with Zephiran and used repeatedly. The rate of the Sigmamotor pump is adjustable and, once set, is constant. Therefore, it was possible to select a rate of infusion between 1 and 100 ml. per minute, and no difficulty was encountered in delivering the two solutions at a constant and equal rate.

The femoral vessels were isolated and cannulated via small tributaries, without appreciable alteration of the main channels. Sampling catheters were placed in the same way. A fine plastic catheter was inserted through a branch of the femoral artery for delivery of the heparin solution, and a similar catheter through a branch of the femoral vein for the protamine. The catheters in the pump were connected to these. The other ends of the pump catheters were attached to the intravenous-infusion tubes.

The level of heparinization in the extremity was determined by protamine titration tests performed on samples of the femoral-vein blood drawn through a catheter inserted distal to the one through which protamine was infused; femoral-artery samples were obtained through a catheter inserted distal to the one through which heparin was added. Systemic heparinization was measured in samples aspirated from an exposed external jugular vein with the use of a glass syringe and a No. 20 needle. A clean, dry syringe was used for each sample. The jugular vein was not cannulated since it would have thrombosed in the absence of systemic heparin effect. Repeated venepunctures were done without altering the continuity of the vessel. Figure 1 shows the infusion technic, and the location of the femoral-vein sampling catheter.

Protamine dilutions in 0.1 ml. of saline solution were placed in clean glass tubes, 12 by 75 mm. The first tube contained saline solution only. The other tubes contained various amounts of protamine as indicated on the vertical axis of the figures. In most cases the concentrations per milliliter of added blood were 25, 50, and 100 microgm. Parallel series of tubes were used for simultaneous titrations on blood from the femoral and jugular veins. After the blood had been added, the tubes were immediately inverted once to mix their contents. They were then left undisturbed at room temperature for fifteen minutes. At the end of that time they were inspected for clotting. A tube was not assumed to be clotted unless we could invert it without displacing the blood. The level of heparin was measured as the lowest concentration of protamine per milliliter of blood that produced a clot within fifteen minutes. This is the figure plotted on the graphs below in the section entitled "Results." This, of course, does not give an absolute measure of the heparin level, but it indicates in a relative sense how close the sample was to being neutralized with protamine in vivo. It was assumed that clotting in the saline control tube meant in vivo neutralization.

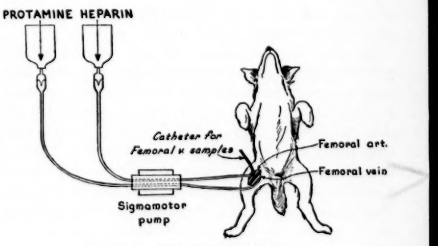


FIGURE 1. *The Infusion Technic.*

RESULTS

Infusion of Heparin Alone

Figure 2 shows the results of titrations when heparin was infused into the femoral artery without simultaneous protamine administration. The rate of flow was slow (Fig. 2) in an attempt to follow the usual technic of regional heparinization. As can be seen from the figure, at that rate of flow no heparin effect was apparent by our technic of measurement for a hundred minutes. When continued administration permitted circulating heparin

*T-6S unit, Model 142X Revco Zero-Max Speed Changer, 1/6-h.p. electric motor, 110 v., 60 cy., 1 phase, available from Sigmamotor, Incorporated, Middleport, New York.

to accumulate, heparin effect was demonstrable in femoral-vein samples but was quickly followed by heparin effect in the jugular-vein samples although at somewhat lower levels. Admittedly, the dilutions of protamine used were such that only large amounts of heparin could be detected, but the experiment demonstrated that heparin accumulated in the blood at low rates of continuous administration and that general heparinization is inevitable with even relatively slow rates of regional heparin infusion. The blood flow in the femoral vein of this dog was probably 200 to 300 ml. per minute. This constitutes a large fraction of the cardiac output, and it is not surprising that the amount of heparin required to prolong the clotting time in the leg is a large fraction of the amount required for systemic heparinization. The animal tolerated the procedure with no signs of toxicity. A total dose of 15 mg. per kilogram of body weight was administered.

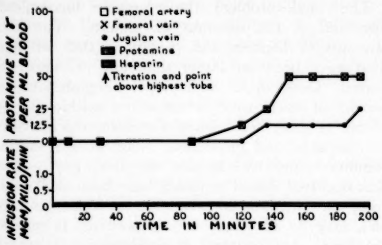


FIGURE 2. *Infusion of Heparin.*

Infusion of Protamine Alone

In this experiment protamine was infused into the femoral vein at rates that began at 0.43 mg. per kilogram of body weight per minute and terminally were stepped up to 1.7 mg. A total dose of 80 mg. per kilogram of body weight was administered in a period of one and three-quarters hours. Blood pressures were recorded continuously,* and no tendency to hypotension occurred. Nor was there any change in the rate of respiration. The dog survived the procedure without any apparent ill effects.

Simultaneous Infusion of Heparin and Protamine

Preliminary in vitro experiments with the lots of heparin and protamine being used indicated that the minimum ratio of protamine to heparin that resulted in a normal clotting time when blood was added to the mixture was 7:5. The heparin and protamine were diluted in 0.1 ml. of saline solution, and 1 ml. of blood was added. Saline solution alone was used as a control.

*Strain Analyzer Model BL-310, available from the Brush Development Company, Cleveland, Ohio.

Simultaneous infusions of heparin and protamine were then performed as outlined above under Materials and Methods. An infusion using equal concentrations of heparin and protamine (250 mg. diluted with 250 ml. of saline solution) resulted in the titration end points indicated in Figure 3. It is obvious that protamine was not being infused at a rate rapid enough to neutralize the heparin, and heparin effect was apparent in the samples of jugular-vein blood. Infusions with a concentration ratio of 7:5 (350 mg. of protamine in 250 ml. of saline solution and 250 mg. of heparin in 250 ml. of saline solution) gave the results presented in Figure 4. The heparin effect in the femoral-vein blood progressively decreased, a fact most easily explained by the assumption of increasing concentration of excess protamine in the circulating blood. A 6:5 ratio of protamine to heparin (300 mg. of protamine and 250 mg. of heparin, each in 250 ml. of saline) gave the results indicated in Figure 5. No heparin effect was apparent in the jugular blood at any point; the femoral-vein blood contained more heparin per milliliter than could be neutralized by 100 microgm. of our protamine preparation. The 6:5 ratio has been used repeatedly with different lots of heparin and protamine, with similar results.

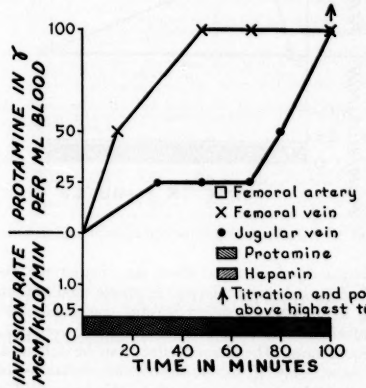


FIGURE 3. *Infusion of Protamine and Heparin in 1:1 Ratio.*

DISCUSSION

Surgeons operating on blood vessels, particularly performing procedures such as endarteriectomy, recognize the need for a technic that will prevent postoperative thrombosis at the operative site. General heparinization carries with it the risk of serious hemorrhage from bleeding lesions elsewhere in the body as well as at the operative site. The usual technic of regional heparinization does not permit

a high enough concentration of heparin within the operated vessel to prevent thrombosis uniformly. We have confirmed the fact that high levels of regional heparinization are associated unavoidably with general heparinization.

With the technic outlined above, it is possible to maintain a very high level of heparin effect in a regional artery and at the same time, by simultaneous infusion of protamine into the corresponding vein, to have no heparin effect in the general circulation. A simplified protamine titration test

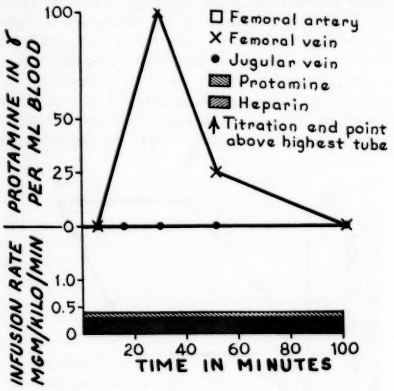


FIGURE 4. *Infusion of Protamine and Heparin in 7:5 Ratio.*

permits a repeated, rapid check on whether the desired effect is being achieved. A simple modification using a Sigmamotor pump permits controlled rates of infusion, with both solutions being delivered at an equal rate. The desired effect can be achieved, of course, only if the ratio of concentrations of heparin and protamine is correct. We have used a number of different lots of both heparin and protamine and have found no variation. Numerous reports in the literature, however, attest to the variability of these preparations,[8,15-18] and although much of this refers to the use of earlier products, it is not wise to rely on the consistency of the effect of preparations in current use. A preliminary in vitro test, as outlined above, can provide a rough approximation of the minimal concentration of protamine needed to neutralize a given amount of heparin. Final adjustments can be made during the course of the perfusions as the results of the titration tests dictate. It has been pointed out on many occasions that the neutralizing ratio of protamine to heparin in vitro is higher than that found necessary in vivo.[17] The in vivo neutralization referred to here, however, is under different conditions from those in our experiments. It refers to the dose of protamine needed in a single injection to neutralize heparin effect created by a single injection given fifteen minutes to an hour previously.

A considerable margin exists between the level of protamine that is the least necessary to neutralize a given amount of heparin and the maximum that can be safely used.[14] This margin allows sufficient time to adjust the concentrations of heparin and protamine in the infusion bottles if this proves necessary.

The final problem that remains incompletely answered is the question of toxicity. The total amounts of heparin and protamine that we have used have been far larger than any previously reported. Doses up to 50 mg. per kilogram of body weight of each were administered within periods of two or three hours without evident toxicity. Since the heparin and protamine were almost entirely combined into an inactive complex, any toxicity that occurred would probably have been due to the complex. No data are available on what this complex may do or where it is deposited. It may be significant that mixtures of protamine and heparin solutions produce a grossly visible precipitate at concentrations that were circulating in our dogs. All we are prepared to say at the moment is that the dogs had no apparent ill effects during the perfusions and survived without evident toxicity.

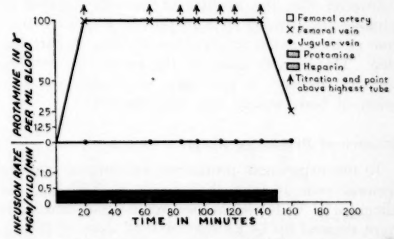


FIGURE 5. *Infusion of Protamine and Heparin in 6:5 Ratio.*

The toxic effect of intravenous protamine alone is well documented.[17,19-23] In our laboratory marked drops in blood pressure have been produced with doses as low as 2 mg. per kilogram of body weight in a single rapid injection.[24] It is therefore of great interest that 80 mg. per kilogram could be infused in a short period without affecting blood pressure or respiration. Apparently, the rate of infusion is more important than the total dose in determining toxic effects.

We are also not in a position to state whether this technic could be carried out for the period of days necessary to prevent thrombosis in an operated artery. The total amounts of heparin and protamine infused would be very much greater than that used in our short runs of two or three hours.

An application of this technic to the artificial kidney has been discovered, however, that uses total doses of heparin and protamine well within the limits used here. This will be the subject of another report.[25]

Summary and Conclusions

A high level of heparin effect was achieved in one extremity of a dog by infusion of heparin into the femoral artery. General heparinization was prevented by the simultaneous infusion of protamine into the femoral vein of the same extremity. The heparin effect in that extremity and in the general circulation was monitored by a simple protamine titration test so that adjustments in the concentrations of the two solutions could be made, if necessary.

No toxic effects were observable in dogs receiving total doses of both heparin and protamine as high as 50 mg. per kilogram of body weight in a period of several hours. Protamine alone was administered by constant infusion in a total dose of 80 mg. per kilogram without affecting the blood pressure or respirations of the dog.

Further work will be necessary before it can be determined whether the procedure can be safely carried out for the period of days necessary to prevent thrombosis after endarteriectomy.

References

1. Murray, D. W. G., Jaques, L. B., Perrett, T. S., and Best, C. H. Heparin and thrombosis of veins following injury. *Surgery* **2**:163-187, 1937.
2. Freeman, N. E., and Gilfillan, R. S. Regional heparinization after thromboendarterectomy in treatment of obliterative arterial disease: preliminary report based on 12 cases. *Surgery* **31**:115-131, 1952.
3. Quick, A. J. On action of heparin and its relation to thromboplastin. *Am. J. Physiol.* **115**:317-333, 1936.
4. Monkhouse, F. C., Drechsler, K., Weber, G., and Fidlar, E. Relation between heparin and thrombin inactivation. *Am. J. Physiol.* **165**:195-204, 1951.
5. Biggs, R., Douglas, A. S., and Macfarlane, R. G. Action of thromboplastic substances. *J. Physiol.* **122**:554-569, 1953.
6. MacMillan, R. L., and Brown, K. W. G. Heparin and thromboplastin. *J. Lab. & Clin. Med.* **44**:378-386, 1954.
7. Douglas, A. S. Action of heparin in prevention of prothrombin conversion. *J. Clin. Investigation* **35**:533-536, 1956.
8. Solandt, D. Y., and Best, C. H. Time-relations of heparin action on blood-clotting and platelet agglutination. *Lancet* **1**:1042-1044, 1940.
9. Keyes, W., and Shaffer, C. F. Hemothorax complicating heparin therapy. *J.A.M.A.* **119**:882, 1942.
10. Jorpes, J. E. *Heparin in the Treatment of Thrombosis: An account of its chemistry, physiology, and application in medicine.* Second edition. 260 pp. New York: Oxford, 1946.
11. Bauer, G. Heparin therapy in acute deep venous thrombosis. *J.A.M.A.* **131**:196-203, 1946.
12. Rieser, P. Effect of roentgen irradiation and other types of injurious agents on capillaries. *Proc. Soc. Exper. Biol. & Med.* **89**:39-41, 1955.
13. Gerbode, F., Osborn, J. J., and Perkins, H. A. Unpublished data.
14. Perkins, H. A., Osborn, J. J., Hurt, R., and Gerbode, F. Neutralization of heparin in vivo with protamine: simple method of estimating required dose. *J. Lab. & Clin. Med.* **48**:223-226, 1956.
15. Jaques, L. B., Charles, A. F., and Best, C. H. Administration of heparin. *Acta med. Scandinav.* Supp. **90**:190-207, 1938.
16. Jorpes, E., Edman, P., and Thaning, T. Neutralization of action of heparin by protamine. *Lancet* **2**:975, 1939.
17. Parkin, T. W., and Kvale, W. F. Neutralization of anticoagulant effects of heparin with protamine (salmine). *Am. Heart J.* **37**:333-342, 1949.
18. Burt, C. C. Clinical application of anti-coagulant drugs. *Brit. M. Bull.* **11**:45-50, 1955.
19. Vartiainen, I., and Marble, A. Effect of subcutaneous administration of protamine (salmine) to rabbits and mice. *J. Lab. & Clin. Med.* **25**:1416-1422, 1941.
20. Reiner, L., de Beer, E. J., and Green, M. Toxic effects of some basic proteins. *Proc. Soc. Exper. Biol. & Med.* **50**:70-74, 1942.
21. Shelley, W. B., Hodgkins, M. P., and Visscher, M. B. Studies on toxicity of protamine. *Proc. Soc. Exper. Biol. & Med.* **50**:300-304, 1942.
22. Portmann, A. F., and Holden, W. D. Protamine (salmine) sulphate, heparin, and blood coagulation. *J. Clin. Investigation* **28**:1451-1458, 1949.
23. Jaques, L. B. Study of toxicity of protamine, salmine. *Brit. J. Pharmacol.* **4**:135-144, 1949.
24. Hurt, R. A. Neutralization of heparin by protamine in extracorporeal circulation. Presented at a meeting of the American Association for Thoracic Surgery, Miami Beach, Florida, May 7-9, 1956.
25. Gordon, L. A., Simon, E. R., Rukes, J. M., Richards, V., and Perkins, H. A. Studies in regional heparinization. II. Artificial kidney hemodialysis without systemic heparinization: description of method using simultaneous infusion of heparin and protamine: preliminary report. *New Eng. J. Med.* (in press).

NONBACTERIAL REGIONAL LYMPHADENITIS ("CAT-SCRATCH FEVER")

Evaluation of Surgical Treatment

Wilfred T. Small, M.D.,* and Ronald C. Sniffen, M.D.†

Worcester, Massachusetts

Nonbacterial regional lymphadenitis, hereafter referred to by the more common designation, "cat-scratch fever," is diagnosed with increased frequency when intradermal test antigen is available. During the past year 7 patients believed to have the disease were admitted to the Memorial Hospital in Worcester. Six were treated by surgical removal of the focus of infection, and these cases form the basis of this report. To our knowledge, there is no report recommending definitive surgery in this disease, although surgery is performed for diagnosis or to drain abscesses.

*Senior clinical instructor in surgery, Tufts University School of Medicine, Boston; junior assistant surgeon, Boston Dispensary; assistant surgeon, Memorial Hospital, Worcester.

†Instructor in pathology, Harvard Medical School, Boston; associate visiting pathologist, Massachusetts General Hospital, Boston; director of laboratories, Memorial Hospital, Worcester.

The clinical characteristics of cat-scratch fever have been described in detail,[1-3] and are summarized here. In the classic case the patient has suffered a cat scratch or bite, though a history of injury is not always obtained. In about half the cases, a skin papule, vesicle or pustule develops within a few days at the site of inoculation. Regional lymphadenitis develops in about four days, but may be delayed as long as seven months.[2] The lymph nodes, usually a conglomerate in the axilla or the cervical or iliac area, become enlarged, tender and painful. Frank suppuration may occur, but there is no deep fixation and the overlying skin is usually not involved. Lymphadenopathy usually persists for two weeks but may continue for six months or longer. There are concomitant systemic symptoms of varying degree,

such as malaise, weakness, chills, fever, anorexia, nausea and abdominal pain. There is usually no correlation between suppuration and the presence or absence of fever. The disease has a predilection for the young: the oldest of our patients was sixteen years of age.

It is important to stress the fact that this is a self-limited disease. On the other hand, the illness usually precludes participation in ordinary activities, such as attending school, and not uncommonly leads to prolonged debilitation. The various antibiotics have no apparent specificity; in none of our cases were they beneficial. It is for these reasons that in selected cases we suggest surgical removal of the involved lymph nodes. We believe that our experience with this small group of cases has justified this approach, since the disease was aborted after the procedure. The temperature returned to normal, well-being was restored, and almost immediately the patient returned to normal activity. One can only speculate on the mechanism of this result. Presumably, the diseased regional lymph nodes harbor the major focus of the infecting agent, which continues to produce systemic symptoms while it is active. Indeed, the skin test antigen is the pus obtained from lymph nodes of a patient with cat-scratch fever. Since there is no known way of inactivating the agent by medical means, surgical removal seems rational.

Case Reports

Case 1. T.R.M. (M.H. 179430), a 6-year-old boy, was first admitted to the hospital on November 4, 1954, because of a painful mass in the right iliac area of 1 week's duration. He had had nightly elevations of temperature to 101°F. during the week before admission.

Physical examination revealed a large, hard, irregular, nodular mass in the right iliac fossa, which extended 6 cm. toward the mid-line. There was no skin injection or fluctuation, but marked tenderness was present with pain when he extended the right leg. The sedimentation rate was 30 mm. per hour, and the white-cell count 11,600, with a normal differential. Other laboratory studies, including tuberculin test, throat cultures, agglutination studies and x-ray examination of the chest, were negative.

The patient was treated with broad-spectrum antibiotics during a hospital stay of 9 days, with nightly temperature elevations to 102°F. He was discharged to be followed at home, but the illness continued with anorexia and fever, and he began to have considerable difficulty in walking. He was readmitted to the hospital 1 week later because of increasing debility, and on the following day abscessed iliac lymph nodes were removed. There was complete amelioration of symptoms after surgery. A small drain was removed on the 3d postoperative day, and he was discharged 5 days later. The temperature was normal from the 1st day.

The diagnosis was, in this case, suggested by the pathology, which was consistent with the changes seen in cat-scratch disease. Questioning before discharge revealed that the patient had several cats, 1 of which had been recently removed because of "distemper." The intradermal skin test was faintly positive at the time of discharge (4-mm. papule).

This case alerted us to the disease. The patient's gratifying response to surgery suggested this course of treatment in future instances.

Case 2. A.J.M. (M.H. 181153), a 4-year-old boy, was admitted to the hospital because of a soft swelling in the right anterior axillary fold of 17 days' duration. The swelling had become progressively larger and more tender. Beginning 10 days before admission erythromycin was given without effect on either the lesion or the constitutional symptoms of malaise, weakness and nightly temperature elevations to 102°F. The patient had a pet cat, which he played with frequently.

Physical examination revealed an acutely and chronically ill boy with a temperature of 102°F. A spherical, firm, nonfluctuant, tender mass, 6 cm. in diameter, was visible and palpable in the anterior axilla on the inferior border of the pectoralis major muscle. There was no involvement of the overlying skin. The intradermal test with cat-scratch antigen was strongly positive. Routine examinations of the blood and urine were negative. The sedimentation rate was 37 mm. in 1 hour. A throat culture was negative for pathogens. On the 7th day the matted, necrotic, suppurating axillary bubo was removed. The wound healed without difficulty; the temperature returned to normal, and the patient was discharged on the 11th postoperative day.

Case 3. R.G.E. (M.H. 187022), a 6-year-old boy, was admitted to the hospital with a history of intermittent fever of 2 weeks' duration and cervical adenopathy.

Physical examination was negative, except for hard, matted lymph nodes in the cervical region on the right that seemed to extend to the sternocleidomastoid muscle. There was a history of a cat scratch on the face 4 weeks previously. The skin test with cat-scratch antigen was negative. Routine blood counts, urinalysis, a tuberculin test, heterophil-antibody agglutination and x-ray study of the chest were negative.

The patient was given 125 mg. of tetracycline every 4 hours for 6 days, with no response in the lymph nodes, and nightly fever continued. He was discharged after 8 days, but the lymph nodes did not subside, and he continued to have malaise and fever. He was readmitted to the hospital 10 days later. The nodes were unchanged, as were the laboratory findings. On the day after admission conglomerate lymph nodes extending into the deep cervical chain were excised.

Convalescence was uneventful. The patient was discharged on the 4th postoperative day in good condition. The temperature was normal, and he rapidly regained strength and well-being.

Examination of the lymph nodes showed a picture consistent with cat-scratch fever. Smears, routine aerobic and anaerobic cultures and cultures for tubercle bacilli on the pus from the nodes were negative.

Perhaps this case should not be included in the face of a negative skin test using an antigen that was subsequently proved to be potent. Operation was performed primarily for diagnosis, since the nodes were grossly consistent with Hodgkin's disease. The dramatic response of symptoms that followed removal of the nodes was gratifying.

Case 4. R.P. (M.H. 189532), an 8-year-old boy, was admitted to the hospital because of a slowly progressive, painless swelling in the right axilla of 3 weeks' duration. Recently, the mass had become painful to touch and limited shoulder motion. He remembered being scratched by a cat a few weeks before the onset of this illness.

On physical examination a movable, hard, nonfluctuant, tender mass, 5 cm. in diameter, was situated in the anterior line of the right axilla; it did not transilluminate. A skin test with cat-scratch antigen was strongly positive in 48 hours.

The hemoglobin was 12.2 gm. per 100 ml., and the white-cell count 9500, with 60 per cent neutrophils, 30 per cent lymphocytes, 7 per cent monocytes and 3 per cent eosinophils. The sedimentation rate was 22 mm. in 1 hour.

On the 4th hospital day the mass was excised, primarily because of pain. A small drain was left in the wound, which was removed on the 3d postoperative day. Subsequently, the patient was symptom free, and he was discharged on the 5th postoperative day.

CASE 5. R.B.M. (M.H. 190077), an 11-year-old boy, entered the hospital because of a slightly tender mass in the left supraclavicular area of 2 weeks' duration. He had experienced general malaise and chills with nightly temperature oscillations between 99 and 102°F. There was a cat in the household, but he had not been scratched to his knowledge. Skin test antigen was applied before entry and was strongly positive (5-mm. papule and 10-mm. flare).

Physical examination revealed a slightly movable mass in the left supraclavicular area that measured 3 cm. in diameter. The overlying skin was not involved, and there was no fluctuation and minimal tenderness.

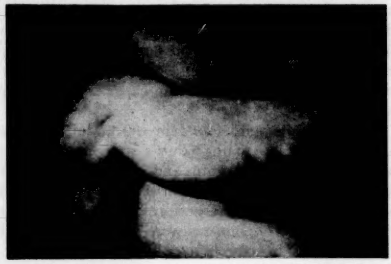


FIGURE 1. *Enlargement of the Axillary and Epitrochlear Lymph Nodes in Case 6.*

X-ray films of the chest were normal. The tuberculin test was negative, as was a urinalysis. Examination of the blood showed a hemoglobin of 13.6 gm. per 100 ml. and a white-cell count of 10,000, with 56 per cent neutrophils, 31 per cent lymphocytes, 7 per cent monocytes and 6 per cent eosinophils. The sedimentation rate was 33 mm. in 1 hour.

On the day after admission the mass was excised. The patient was discharged on the 1st postoperative day to be followed on an ambulatory basis. He was entirely asymptomatic after removal of the lymph nodes.

CASE 6. E.R.M. (M.H. 190614), a 16-year-old boy, was admitted to the hospital because of tender swellings in the left epitrochlear and axillary areas of 5 days' duration. There had been no fever or intercurrent illness.

Physical examination revealed 2 visibly distinct lymph nodes, each measuring about 2 cm. in diameter in the left epitrochlear region. There was a mass, 4 by 3 cm., in the left axilla that was not adherent to the deep structures or overlying skin (Fig. 1). In addition a hyperkeratotic papule, 3 by 2 mm., was noted on the left hypothenar eminence. Apparently, this lesion had been present for some weeks; the patient was very vague but thought that it might have been caused by a splinter.

Routine blood studies and urinalysis were negative. The heterophil-antibody agglutination was positive in a dilution of 1:14, and agglutination for tularemia was negative; the blood Hinton test was also negative. The skin test with cat-scratch antigen was positive in 48 hours (7-mm. papule, 20-mm. flare). On the 5th hospital day the epitrochlear lymph nodes, the axillary mass and the lesion on the hypothenar eminence were removed. There was primary wound healing, and the patient was discharged asymptomatic on the 4th postoperative day.

CASE 7. R.D.T. (M.H. 191051), a 4-year-old girl, entered the hospital because of general malaise, evening temperature elevations and a right-sided parotid swelling of 7 weeks' duration.

Physical examination revealed a chronically ill child with a 3-cm. mass over the right parotid gland. The temperature was normal.

Laboratory studies, including a tuberculin test, heterophil-antibody agglutination and routine blood and urine examinations, were within normal limits. A test with cat-scratch antigen was strongly positive in 48 hours. The parents reported that the mass had been subsiding during the week before admission.

Because of the location of the mass and the fact that the disease was abating, excision was not advised. When the patient was seen 2 months later the mass had broken down and drained spontaneously. Drainage persisted for 2 weeks and was then intermittent for 4 months. At the end of that time the lesion had healed. (In retrospect it might have been better to have resected the lesion in the 1st place.)

The anatomic changes in the diseased lymph nodes did not differ from those previously recorded,[4] nor was there sufficient variation between the cases to warrant separate description. A reasonably clear-cut sequence of inflammatory changes had occurred that differed from case to case only in the degree of evolution or healing. The quality of the inflammatory reaction in cat-scratch disease, although not specific, is sufficiently characteristic to allow one to entertain the diagnosis. Therefore, to arrive at a working conclusion, one leans heavily on the history,

FIGURE 2. *Subcapsular Zone of a Lymph Node, Showing Nonspecific Hyperplasia, with Large, Active Germinal Centers.*

skin tests and negative agglutinations and the inability to grow or see a causative agent. The differential diagnoses include bacterial lymphadenitis (tularemia, brucellosis), tuberculosis, sporotrichosis and lymphopathia venereum.

In the cases reported above, the excised lymph nodes were matted together, the largest aggregation being 3 cm. in diameter. The sectioned surfaces were

firm and fleshy and often hemorrhagic and traversed by irregular fibrous septa. Usually, the surface was punctuated by areas of softening from which thick, yellow pus could be expressed.

Microscopically, it seemed that all the visible phases of the inflammatory process could be appreciated in each node or group of nodes.

In the initial stages of the process the nodes showed a general hyperplasia, with active germinal centers in the cortex, and reticular hyperplasia (Fig. 2). Subsequently, foci of reticular cells developed to form small "tubercles" with or without an admixture of lymphocytes, plasma cells and neutrophils. The surrounding lymphoid tissue was also infiltrated with plasma cells, neutrophils and sometimes a considerable number of eosinophils. Thereafter, the number of neutrophils increased in the tubercles, and the cytoplasm of the reticular cells became vacuolated. This change was followed by central necrosis to form small abscesses containing neutrophils and cellular débris. In some cases the nodes were removed at this stage, but in others large irregular abscesses had developed apparently by extension or fusion of neighboring foci. In the abscesses there was total disintegration of the tissue, and the reticulum and blood vessels had disappeared. In the most characteristic phase, the areas of necrosis were surrounded by a clear-cut zone of epithelioid cells of pleomorphic character and ill defined cytoplasmic boundaries (Fig. 3). Occasionally, giant cells of the Langhans or foreign-body type were present, but these were never numerous. The early reparative reaction around the tubercles consisted of fibroblast formation and collagen deposition with the various inflammatory cells in the interstices. Some nodes contained large areas of fibrosis and small foci of dense collagen, presumably the end result of the process. It was usual to find perinodal fibrosis and chronic inflammation, and occasionally small abscesses; in a few nodes a point of capsular destruction was encountered.

FIGURE 3. *Abscess Containing Neutrophils and Cellular Débris and Encompassed by a Well Defined Zone of Epithelioid Cells.*
The surrounding tissue shows a chronic inflammatory infiltrate, with early fibrosis.

No organisms were found in the nodes with the use of appropriate stains (Putt's stain for acid-fast bacilli, Brown–Brenn stain and periodic-acid-Schiff stain for yeasts and fungi). In the 4 cases in which bacteriologic studies were performed on pus from the excised nodes, no organisms were found on smear or demonstrated by aerobic or anaerobic cultures. Tubercle bacilli were not cultured in the only case thus examined.

The hypothenar skin lesion that was assumed to be the portal of entry in Case 6 showed a nonspecific reaction, with hyperkeratosis, acanthosis, mild pseudoepitheliomatous hyperplasia and a heavy infiltrate of lymphocytes, plasma cells and histiocytes in the upper dermis.

DISCUSSION

As noted, the apparent incidence of cat-scratch disease will increase when more intradermal antigen is available. Before our access to it, no case had been diagnosed at the hospital. Since that time 7 cases have been recognized in the past year, and this experience will be reproduced many times in like areas throughout the country. Presumably, the disease has been present for centuries, masquerading under other names, the most common being nonspecific adenitis or glandular fever. Its benign course in most cases has attracted little attention. Despite this benignity, major complications, such as encephalitis, have been reported although these are rare.[5]

Our experience with surgical removal of the buboes has been most gratifying, though the criteria for operation must be strict, for the disease is self-limited. One must be as certain of the diagnosis as possible from an evaluation of the history, physical findings and the result of the intradermal antigen test. To justify surgical excision of the nodes, the patient should have had symptoms for several weeks and should be unable to carry on normal activity. A good cosmetic result must be assured, and the procedure limited to a single group of abscessed nodes. Because the tissue is bacteriologically sterile, total

excision and closure seem to be preferable to drainage. The prime object in surgical intervention is to abort a potentially prolonged illness with a minimum risk to the patient.

Summary

Six cases of cat-scratch fever treated by excision of the involved lymph nodes are presented. After removal of the major focus of inflammation, constitutional symptoms rapidly disappeared even in those patients with prolonged debilitation. The rationale and indications for this type of therapy are discussed, and the histology of the condition reviewed.

We are indebted to Dr. Lawrence J. Kunz, of the Massachusetts General Hospital, for supplying the antigen for use in this study and to Drs. John P. Chandler and Edwin B. Seelye for permission to include, respectively, Case 4 and Case 6.

References

1. McGovern, J. J., Kunz, L. J., and Blodgett, F. M. Nonbacterial regional lymphadenitis ("cat-scratch fever"). *New Eng. J. Med.* **252**:166-172, 1955.
2. Daniels, W. B., and MacMurray, F. G. Cat scratch disease: report of 160 cases. *J.A.M.A.* **154**:1247-1251, 1954.
3. Greer, W. E. R., and Keefer, C. S. Cat-scratch fever: disease entity. *New Eng. J. Med.* **244**:545-548, 1951.
4. Winship, T. Pathologic changes in so-called cat scratch fever: review of findings in lymph nodes of 29 patients and cutaneous lesions of 2 patients. *Am. J. Clin. Path.* **23**:1012-1018, 1953.
5. Stevens, H. Cat-scratch fever encephalitis. *Am. J. Dis. Child.* **84**: 218-222, 1952.

LARYNGOPHARYNGEAL CANCER*

Five-Year Results after X-Ray Therapy

C. C. Wang, M.D.†

BOSTON

THIS report presents a study of a group of patients in whom malignant neoplasm had arisen in the epiglottis, aryepiglottic fold, arytenoid, pyriform sinus and postcricoid. These tumors, often called laryngopharyngeal cancer or "extrinsic cancer of the larynx," may invade the endolarynx or extend to the lateral pharyngeal wall and base of the tongue, and at times the disease is so extensive that the exact site of origin may be difficult to determine. Cancers arising in the laryngopharynx are quite different from those of the endolarynx. They carry a high mortality, recur frequently after operation and metastasize early; often, they are not discovered until late in the disease.

From 1931-1950, inclusive, approximately 150 patients with laryngopharyngeal cancer were treated with x-rays in the Department of Radiology at the Massachusetts General Hospital. This group, with a minimum five-year follow-up period, forms the basis of the present investigation. Owing to the lack of an internationally accepted classification, one used by Harris et al.[1] has been slightly modified and followed. So far as possible the patients have been grouped according to the extent of the tumor involvement, as follows:

Group A. Anterior lesions (epiglottis).

Group B. Posterolateral lesions (arytenoid, aryepiglottic fold, pyriform sinus and postcricoid).

Group C. Extensive lesions, both anterior and posterolateral.

The therapeutic results after x-ray have been evaluated.

*From the Department of Radiology, Massachusetts General Hospital.

†Teaching fellow in radiology, Harvard Medical School; clinical fellow, Department of Radiology, Massachusetts General Hospital.

Age and Sex

Like cancer of the endolarynx,[2] the laryngopharyngeal tumors were found predominantly in the elderly males, only 8 out of 150 patients, or 5 per cent, being females. Of the entire group, 85 per cent were fifty years of age or over; only 3 patients were below forty years. Histologically, all the lesions were proved to be squamous-cell carcinoma.

Symptoms

The laryngopharyngeal cancers produced few if any early symptoms and commonly metastasized before a diagnosis could be made and treatment started. The chief complaints in order of frequency were hoarseness, dysphagia, sore throat and cough, with occasional blood-streaked sputum. Difficulty in breathing, sufficiently severe to necessitate tracheotomy, often ushered in the discovery of the growth.

Diagnosis

The establishment of the diagnosis and exact localization of the tumor called for adequate visualization by indirect or direct laryngoscopy or both. Soft-tissue roentgenography of the neck and barium-swallow study were helpful in delineating the tumor; tissue biopsy confirmed the diagnosis. Careful palpation of the neck revealed or ruled out obvious lymph-node metastasis.

Therapy

In the past twenty years x-rays have been employed at the Massachusetts General Hospital in the treatment of laryngopharyngeal cancer; 200-kv. radiation filtered with 0.5 mm. of copper at 50 cm., target-skin

distance being used. The technic has been slightly modified and improved from time to time. Two direct opposing lateral portals with a field of 6 by 8 cm. or 8 by 10 cm., delivering a dose of 4500 to 5000 r to the tumor at the rate of 200 r per day in five or six weeks, were employed. Occasionally, an additional anterior portal of entry was required. During the course of treatment frequent inspection of the irradiated area was necessary to observe the response of the tumor. Since the advent of supervoltage therapy (1000-2000 kv.) a cancerocidal dose can be delivered to a tumor-bearing area through a single portal with a minimal degree of skin reaction. This is particularly beneficial when a unilateral cervical metastasis is found at the beginning of treatment, the primary growth as well as the secondary lesions being irradiated concomitantly within a single portal of entry. Interstitial radium implantation was occasionally necessary for residual tumor in the lymph nodes, and radical neck dissection was required when the primary growth had been controlled.

TABLE 1. *Five-Year Results of X-Ray Therapy of Laryngopharyngeal Cancer (1931-1950).*

TYPE OF TUMOR	TOTAL CASES TREATED	PATIENTS DEAD WITH DISEASE	PATIENTS SYMPTOM FREE AFTER 5 YR.
Group A: anterior lesions	29	20	9(31%)
Group B: posterolateral lesions	65	55	8(12%)
Group C: extensive lesions	56	48	10(17%)
Totals	150	123	27(18%)

TABLE 2. *Results of X-Ray Therapy in Group B (Lesions Small and Limited to a Single Structure).*

SITE OF TUMOR	TOTAL CASES TREATED	PATIENTS DEAD WITH DISEASE	PATIENTS SYMPTOM FREE AFTER 5 YR.
Aryepiglottic fold	11	8	3(27%)
Pyriform sinus	12	9	3(25%)
Postcricoid region	2	1	1(50%)
Totals	25	18	7(28%)

The results of radiation therapy are summarized in Table 1. Of the entire group 9, or 31 per cent, of 29 patients in Group A (anterior lesions) survived for five years after radiation without symptoms. Of 65 patients in Group B (posterolateral lesions) 8, or 12 per cent, survived for five years symptom free. When the lesions were so extensive that both anterior and posterior structures were invaded (Group C) 10 out of 56 patients, or 17 per cent, were considered cured for five years.

Table 2 shows the therapeutic results in Group B patients in whom the lesions were found to be small and limited to a single structure. Of the 11 patients with tumor arising in the aryepiglottic fold and the 12 in the pyriform sinus, 3 of each, or 27 and 25 per cent, respectively, survived for five years after irradiation.

As is probably true in all cancer therapy, lymph-node metastasis has tremendous bearing on the prognosis (Table 3). Of the entire group treated (150 patients) 78, or 52 per cent, exhibited lymph-node metastases at the beginning of therapy. Of these 78 patients only 6, or 8 per cent, survived for five years. On the other hand 21, or 29 per cent, of 72 patients in whom metastases were not apparent at the time of treatment lived for five years.

TABLE 3. *Results of X-Ray Therapy in Relation to Lymph-Node Metastases in Entire Group.*

TYPE OF TUMOR	TOTAL CASES TREATED	CASES WITHOUT METASTASES		CASES WITH METASTASES	
		NO. TREATED	PATIENTS SURVIVING FOR 5 YR.	NO. TREATED	PATIENTS SURVIVING FOR 5 YR.
Group A: anterior lesions	29	16	7(44%)	13	2(15%)
Group B: posterolateral lesions	65	27	7(26%)	38	1(3%)
Group C: extensive lesions	56	29	7(24%)	27	3(11%)
Totals	150	72	21(29%)	78	6(8%)

In Group A, the epiglottic lesions, when no lymph-node metastasis was evident at the time of treatment, 7 out of 16 patients, or 44 per cent, survived for five years, in contrast to 15 per cent of 13 patients with metastasis.

TABLE 4. *Results in Relation to Lymph-Node Metastases in Group B.*

SITE OF TUMOR	TOTAL CASES TREATED	CASES WITHOUT METASTASES		CASES WITH METASTASES	
		NO. TREATED	PATIENTS SURVIVING FOR 5 YR.	NO. TREATED	PATIENTS SURVIVING FOR 5 YR.
Aryepiglottic fold	11	3	2(67%)	8	1(13%)
Pyriform sinus	12	8	3(35%)	4	0
Postcricoid region	2	1	1(100%)	1	0
Totals	25	12	6(50%)	13	1(7%)

In Group B (Table 4) there were 25 patients whose tumors were considered to be relatively small, chiefly confined to the aryepiglottic fold, pyriform sinus and postcricoid region. In these small lesions when no metastasis was evident at the time of therapy, 6 out of 12 patients, or 50 per cent, were found to be alive at the end of five years, in contrast to 1 out of 13 patients, or 7 per cent, with metastasis.

In Group C (Table 3) 7 out of 29 patients, or 24 per cent, without lymph-node metastases lived for five years, and only 3 of 27, or 11 per cent, with metastatic disease survived for the same period.

Summary and Conclusions

The therapeutic results of laryngopharyngeal cancer reported in the literature vary considerably,[1,3-6] but in general are universally poor. This has been further substantiated by the present study of 150 patients treated by radiation at this hospital. The lack of therapeutic success is probably due to the nature of the neoplasm, the early metastasis and the delayed institution of therapy because of the late recognition of the growth. Surgical and radiotherapeutic methods will have to be improved if satisfactory control of the disease is to be achieved.

It cannot be overemphasized that early recognition of the lesion and prompt institution of treatment are vital for cure since the control of laryngopharyngeal cancer by irradiation is adversely related to the extent of involvement and the presence of cervical metastases. Treatment of the early lesions, particularly those of the epiglottis (Group A), therefore, may be attended with fairly satisfactory results.

In the management of a given neoplasm in this region, the understanding of its nature, proper evaluation of its site, extent and lymph-node metastases and the general condition of the patient should be taken into consideration before any course of treatment is planned. In the relatively aged and feeble patient with advanced lesions, palliation is probably all that should be offered. This is given with the intention of alleviating pain and infection and prolonging, if possible, a useful and comfortable life. On the other hand, in patients with good health and early cancer, vigorous radiation therapy aimed at cure is justified.

The results of supervoltage radiation in carcinoma of the laryngopharyngeal region await further evaluation.

References

1. Harris, W., Silverstone, S. M., and Kramer, R. Roentgen therapy for cancer of larynx and laryngopharynx: 20 years' experience. *Am. J. Roentgenol.* **71**:813-825, 1954.
2. Wang, C. C., and O'Donnell, A. R. Cancer of larynx: five-year results, with emphasis on radiotherapy. *New Eng. J. Med.* **252**:743-747, 1955.
3. Blady, J. V., and Chamberlain, W. E. Treatment of cancer of larynx by roentgen irradiation: report of 5 year end-results. *Am. J. Roentgenol.* **51**:481-495, 1944.
4. Martin, H. Cancer of larynx. In *Nelson's Loose-Leaf Surgery.* Vol. 8. New York: Nelson, 1947. Pp. 431-505.
5. Orton, H. B. Symposium: carcinoma of larynx: treatment of extensive carcinoma of larynx. *Laryngoscope* **61**:496-510, 1951.
6. Pizon, P. Roentgenthérapie des cancers du larynx et du laryngopharynx. *Presse méd.* **62**:1386, 1954.

SPECIAL ARTICLE

THE HARVARD MEDICAL SCHOOL, 1906-1956*

Edward D. Churchill, M.D.†

BOSTON

EARLY in the autumn of 1868 two young Boston doctors met in Paris almost as it were by chance. One was J. Collins Warren, who had spent a summer vacation mountain climbing in Switzerland and was looking toward a return to Berlin to continue his studies in the laboratory of Julius Cohnheim. Shortly before, Cohnheim had demonstrated the ability of the white cells of the blood to pass through the capillary vessels, thus affording a fresh and dynamic insight into the behavior of living tissues in inflammation. Cellular pathology was the keynote of the new medical science in Germany, and young "Coll" Warren had been immersing himself in it, excited by the rational point of view it brought to the surgery of the period. When the fall term was about to begin, however, Cohnheim was called to Kiel, and although Warren received an invitation to follow him to that city, a decision was made to remain in Paris instead.

The other young doctor, Henry Pickering Bowditch, was a few years older than Warren, but the Civil War had so dislocated personal educational plans that the two became medical contemporaries. On arrival in Paris, Warren found Bowditch working in the laboratory of Claude Bernard at the Collège de France. Bernard had achieved his world-wide reputation, and although growing old was still absorbed in his research on the function of the sympathetic nervous system. Bowditch suggested that Warren settle down with him at the Collège de France and study under Louis Ranvier, a young morphologist who was gaining recognition rapidly by his work on the finer structure of nerves. Bernard and Ranvier, although pursuing entirely different lines of work, were close neighbors in the laboratory, and during the winter Warren heard much about the new outlook of physiology. He thus became one of the very first surgeons to grasp the fact that disturbances in function are as important to the practical art of the surgeon as alterations in structure. This experience in Paris kindled an enthusiasm for surgery as a biological science that was to carry Warren through the long and contentious period when the scientific doctor was regarded with suspicion or active hostility by his colleagues of the craft.

The companionship between Coll Warren and

*Alumni Day Address, presented at Harvard Medical School, May 31, 1956.

†John Homans Professor of Surgery, Harvard Medical School; chief of the General Surgical Services, Massachusetts General Hospital.

Henry Bowditch starting under these circumstances became cemented into a friendship that lasted through life. It was on the foundation of this friendship that the Harvard Medical School of 1906 was planned and built. In fact one may truthfully say that the School was conceived that winter in Paris in the laboratories of the Collège de France, for early in 1869 Bowditch wrote to his mother:

> I have been building all sorts of laboratories and medical schools in the air. In this labor I have been materially assisted by Coll. Warren who is quite convinced that something ought to be done to raise the standard of scientific education in our community. I mean, of course, particularly medical science.

Bowditch and Warren were still in Paris in the spring when an event took place in Boston that also turned out to be of great importance to the Medical School. On March 10, 1869, the overseers of the University met in the old Medical School building on North Grove Street to approve the granting of degrees to about seventy medical students. This building, supported on piles, extended over the tidewater marsh on the site of what is now the gently sloping approach to the main entrance of the Massachusetts General Hospital. A youthful member of the Faculty of the new Massachusetts Institute of Technology recently had been elected an overseer, and he was present at this meeting. During the proceedings the door of the room opened, and the Reverend George Putnam beckoned to this new overseer. On stepping out into the corridor, he was informed that the Harvard Corporation wished to elect him to the presidency: would he accept? And thus Charles W. Eliot, after a delay occasioned by the cautious overseers, became the president of Harvard University. His perception of the contribution that science held in store for the healing arts was to align Eliot's vigorous academic statesmanship with the visions of Bowditch and Warren.

Dr. Warren returned from his European studies to occupy himself with a small practice at Number Two Park Street and begin the slow climb up the surgical ladder at the Medical School and the Hospital. President Eliot invited Dr. Bowditch back to Harvard, where he became the first member of the Medical Faculty who did not choose to practice medicine. In 1871 a small attic was built on the North Grove Street School to provide three rooms for laboratories. Their windows looked out across the Hospital yard to the dome of the Bulfinch Building, where, just twenty-five years before, it had been shown that a product of the science of chemistry could be put to direct and practical use in the control of human suffering. Ether was one of the first substances transferred from materia chemica to materia medica, and this event had made a great impression on the practical-minded American doctor.

In the newly constructed attic one small laboratory was called the "microscope room," and in it Oliver Wendell Holmes taught histology. In the remaining two rooms Henry Bowditch devoted his full working day to investigation and instruction in the newly formed Department of Physiology. This laboratory, Dr. Walter B. Cannon has said, can be regarded as the first laboratory of experimental medicine on this continent because of the breadth of the investigations there pursued.

The move of the Harvard Medical School to Boylston Street in 1883, although considered a great event at the time, must be looked upon in retrospect as simply marking a transition period. The additional laboratory space made available proved merely a temporary easement of growing needs. In fact, it was recognized that the building was inadequate even before its construction was complete.

The planning for the School of the past five decades began in the closing years of the last century. Among the Faculty it became known as "the great undertaking." Dr. Frederick Shattuck recalled the story at a dinner of the Medical Faculty on April 24, 1912:

> It was, I think, in 1898 that an informal meeting was held at Dr. Warren's house, and there he and Bowditch, whose spirit watches over and abides with us, unfolded their prophetic dream. They saw this spot with its beautiful and ample school buildings, set about, as it soon will be, by a group of affiliated institutions for the relief, study and the prevention of disease. I, doubting Thomas that I was, confess to having classed them as general paretics, typical megalomaniacs. Rarely have the visions of youth and the dreams of age been so united, so fully and quickly realized in fact. May we not read a deep meaning into the fact that the court of the school buildings is opened to the east, and, through the Avenue Louis Pasteur, is flooded by the rays of the rising sun? . . . Never have the sources of inspiration been so overflowing as they are to-day. The irrigating channels are well laid; the ground is ready; the laborers are keen and skilled; the crop is assured.

Thus, after the completion of its great undertaking the Faculty, like the God of the Old Testament, looked upon its work and saw that it was good.

At the time of President Eliot's retirement, in a citation for the degree of doctor of medicine, *honoris causa*, it was said that he had found the Medical School brick and left it marble. The buildings of the School are not important in themselves; they are significant only as they express the design and purpose of the University activity that goes on within. The buildings may be likened to the exoskeleton of a living organism, and this carapace, which extends to the right and the left, reveals certain ideas that were uppermost in the minds of the planners at the beginning of the century — ideas about medicine, medical research and medical education.

Planning can be no better than the ideas or assumptions upon which it is based, and before one considers how well the blueprint of the planners may have withstood the impact of reality during fifty years, it is necessary to examine more closely just what they had in mind. Attention will be focused on the three men already identified, Charles W. Eliot, Henry P. Bowditch and J. Collins Warren. In the

reverent words of Dr. Shattuck, it may be assured that their spirits watch over and abide with us today.

Uppermost in the minds of all three was the task phrased by Bowditch in his 1869 letter — the elevation of the standards of medical science in this community. The institution they sought to establish was described by Warren as a "great and ideal university medical school." All three as young men had been inspired by the universities of Europe, but the new Harvard Medical School was not merely a transference of European educational patterns to the Fenway. The impressions received as young men had been seasoned by the perspective of some thirty years spent in close grips with the realities of a university and medical school in the American tradition; the Paris days of building laboratories and schools in the air were long past.

Charles W. Eliot

President Eliot's clear vision of what the scientific method could bring to medicine was shared by Warren and Bowditch. The healing arts of this country were lagging behind, and their practitioners were not only unscientific but antiscientific. In his efforts to bring the standards of the graduate departments of the University to an acceptable level, Eliot had observed the Hopkins development closely and with keen interest; indeed, his advice was sought at many points. Later, he confessed that his efforts to stimulate graduate education at Harvard had met with an indifferent response until the example of the Hopkins forced his faculties to face the problem in a wholehearted manner. The emergence of the Hopkins between 1875 and 1895 had placed professional education within a scientific setting and elevated medical studies to a university graduate-school level for the first time in America.

When exploring the backwardness of the healing arts in this country for Mr. Rockefeller, Frederick T. Gates* found that "research had been left to shift for itself, dependent altogether on such chance time as a rare spirit, without facilities, might steal from his practice." The Rockefeller Institute was founded in 1903. Mr. Gates tells the following anecdote about Mr. Eliot:

> One day I chanced to be walking down Broadway with President Charles W. Eliot of Harvard. We were talking about the Rockefeller Institute and I ventured to confess to him that to me the institute was the most interesting thing in the world. "Nothing," said I, "is to me so exciting, so fascinating as the work the institute is doing."
>
> Dr. Eliot stopped short in the street and turned to me and said with emphasis and emotion, "I myself feel precisely so. The Rockefeller Institute is to me the most interesting thing in this world."

It is stated in contemporary sources that the leaders of the Medical Faculty at Harvard "envisioned a group of more or less detached 'institutes' devoted to anatomy, physiology, and the other great departments of medicine." This was a pattern that had been scientifically productive on the Continent and was reflected in part in the structure of the Rockefeller Institute. At Harvard the institutes were to carry on preclinical education and were identified as the disciplines of the vocational course of studies.

Henry P. Bowditch

Early in his career at the Medical School Bowditch had seen the need to devote a large share of his energies to educational reform. A clear expression of his outlook on medical studies can be found in his presidential address entitled "The Medical School of the Future" and delivered at the Congress of American Physicians and Surgeons in 1900. The address makes timely reading today. It was not merely the growing mass of factual knowledge that led Bowditch to examine the compulsory curriculum of medical studies with a critical eye. Entire fields of knowledge were appearing with systematized theoretical and applied contents, ready for the uses of education. During the period in which the present School was planned and built, the most notable emerging field of knowledge came with the germ theory of disease and the doctrine of specific etiology.

Bowditch tried to persuade his colleagues to loosen the bonds of the rigid vocational curriculum and adapt medical education to the powers of the individual mind to be educated. In the case of advanced students, the choice of the individual was to be a determining factor in the selection of studies. A course of medical study, according to Bowditch, needed to distinguish between what is *essential* for *every* student to know and what is *desirable* for *certain* students to know. All members of a faculty will agree to this principle — with the reservation that "what I teach is essential; what you teach is (scarcely) desirable."

Bowditch's effort to bring some measure of freedom from compulsion to the medical student was, of course, grist to the mill of President Eliot, sponsor of the elective system. The President, at a dinner of the Harvard Medical Alumni Association in 1895, had brought forward a compelling train of logic:

> There ought to be in the Harvard Medical School an extended instruction far beyond the limits of any one student's capacity. This involves, of course, some optional or elective system within the school itself, whereby the individual student should take what is, for him, the best four years' worth, the faculty supplying teaching which it might take a single student eight, twelve or twenty years to pursue.

In these two sentences Eliot pointed up the difference between a course of studies dominated by vocational purposes and one befitting a university. Computed mathematically, this "Eliot Index" would be the ratio between the educational opportunities a

*Acknowledgment is made to the editors of *American Heritage* [Vol. 6, April, 1955, pp. 72 and 73 — "The Memoirs of Frederick T. Gates"] and to Mr. Russell C. Gates for the privilege of including these quotations.

faculty spreads before its students and the sequence of courses that can be encompassed by an average student in four years.

J. Collins Warren

J. Collins Warren, the third of the trio under discussion, had talked with Joseph Lister, and with him had walked the wards of the Glasgow Royal Infirmary. Warren returned from Europe in 1869,

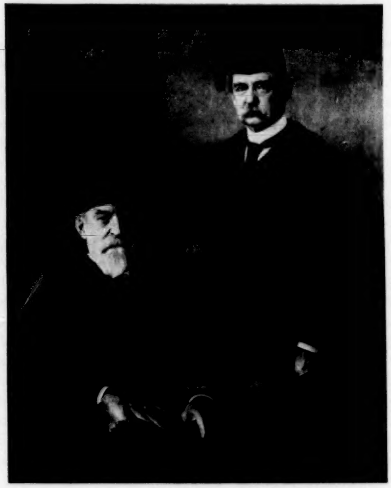


Figure 1. *Professors Henry P. Bowditch (Seated) and J. Collins Warren.*

exuberant with an awareness that, in his own words, it was time "to cast off much that was old and prepare ourselves for the dawn of a science which was to revolutionize medicine." What actually happened was that the young Dr. Warren took his place on the amphitheater benches, where he maintained a respectful silence while his elders performed the Saturday morning operations in the same old way. When he ventured to propose a trial of the Lister dressings, of which he had brought back an abundant supply, he was informed coldly that the "carbolic acid treatment" had already been tried and discarded. Later, when he attempted to introduce sterilization by heat, the key to so-called "aseptic surgery," his efforts met with frustration, and the credit for this discovery went elsewhere.

The staff organization of the old hospital provided little opportunity for the pursuit of clinical studies. The method of instructing students centered on their memorizing the rules of the practical art. In 1893 Warren publicly deplored the "old-fashioned prejudice which resented the intrusion of students into the hospital wards. The theory of the trustee of that time was: This money was given for the cure of patients and not for the education of physicians. They could not be persuaded that the two interests were identical."

Medical School and Teaching Hospital

It is understandable why uppermost in Warren's mind when he helped launch the great undertaking was the bringing about of a more intimate relation between medical school and teaching hospital. A change was needed in the procedure of staff appointments of those responsible for teaching. Significant advances had been achieved by introducing the preclinical years of study, but the road toward more effective clinical instruction was blocked by physicians and surgeons who, by donating their services to charity patients, had built up vested rights on the hospital wards. Promotions within the staff were based on seniority.

At the Hopkins this state of affairs had not been encountered in the establishment of a new hospital and it had been found possible to call men from other cities to professorial chairs in clinical subjects, just as with other university appointments. The Johns Hopkins had been able to attain world-wide celebrity by selecting unusual talent wherever it happened to be found; at Harvard teachers of the clinical subjects were recruited among men who had established economic roots in the community and had secured hospital staff appointments.

Early in 1890 the University had opened negotiations with the trustees of the Massachusetts General Hospital in which the privilege of nomination for a Hospital appointment was sought in connection with the academic departments of medicine and surgery. After lengthy deliberation, however, the trustees of the Hospital were unable to come to a favorable decision on a matter involving so radical a change and opposed by so many staff members. The Faculty then considered raising funds to establish and maintain a hospital under complete control of the University, but the magnitude of the task made them reluctant to proceed with such a plan.

It was about this time that the keen eye of Dr. Bowditch discovered a possible solution of this problem of clinical facilities in the will of Peter Bent Brigham, who had died many years before. The date at which his large bequest for the building of a hospital would mature was growing near. The meeting at Dr. Warren's in 1898 has been described, and in 1899 the Faculty made up its mind to obtain a plot of land that would be sufficiently large to accommodate a group of buildings for the School and to provide room for the Brigham and other hospitals that might be induced to build within the same area.

The selection of the most appropriate site was

perplexing, for if the trustees of the Brigham Hospital were to be induced to become neighbors of the School, a location within Suffolk County was required. This stipulation in the will excluded the vacant tract on the north bank of the Charles River now occupied by the Massachusetts Institute of Technology. Warren, among others, considered the site adjoining Soldier's Field now occupied by the Harvard School of Business Administration to be ideal. The advantage of bringing the Medical School into close proximity to the other departments of the University was discussed, but its importance considered secondary to other considerations. Before the construction of the Charles River Dam in 1910, the spring tides flooded the vicinity of Soldier's Field, and such a location for a hospital might well be questioned on hygienic grounds. Also, the Brigham Hospital was to be for the sick poor of Boston, and this site was inaccessible and remote from the congested areas of the city. As Warren wrote: "Any action on the part of a great educational institution seemingly to appropriate for its own uses a charitable bequest of many millions of dollars intended for the sick poor of Boston would be regarded with suspicion."

And so the 26 acres of the old Francis estate, which had been a country residence and showplace on the shore of the original Back Bay, were purchased for the great undertaking of the new Medical School and the hospitals that were to become its neighbors. The Medical Faculty decided to "go it alone," remote from the other departments of the University, as the price for personnel control in the realm of clinical instruction.

The desired hospital relations came about of their own accord, for in 1908, two years after the new School had opened, a break in the tight pattern of staff organization took place at the Massachusetts General Hospital. Dr. Frederick C. Shattuck, Jackson Professor of Clinical Medicine at Harvard and visiting physician at the Hospital, was given a continuous service with Dr. Richard C. Cabot as his assistant. In 1911 the post of surgeon-in-chief was created for Dr. Maurice H. Richardson. In 1912 Dr. David L. Edsall was called from Washington University to succeed Dr. Shattuck and assume the Jackson Professorship of Clinical Medicine.

By 1912 ground was broken for the new Children's Hospital, the Peter Bent Brigham Hospital was under construction, and either built or planned for in the immediate neighborhood were the Infants' Hospital, the Collis P. Huntington Memorial, the Nutrition Laboratory of the Carnegie Institution, the Dental School and the Angell Memorial Hospital for Animals. An editorial writer in the *Boston Medical and Surgical Journal,* under the title "The Development of a Medical Center," referred to a "remarkable center of medical education, practice and research." Although the first half of this century was to see many medical centers spring up throughout the country, Harvard had already formulated a policy of much broader scope.

The triennial dinner of the Harvard Medical Alumni Association on May 22, 1912, was addressed by President A. Lawrence Lowell, who had taken up the duties of the presidency three years before. Mr. Lowell placed high value on intellectual prowess and believed that excellence is not won by students or by faculty merely from being afforded an opportunity to develop. In his mind was the belief that productive scholarship is distilled from the struggle of competitive effort and a process of intellectual attrition. With this conviction, it is not surprising that the new president did not allow his vision to be confined by the restricted concept of a medical center; he saw the opium of complacency in the insular isolation that might overtake the Medical Faculty. Mr. Lowell spoke of the present as a time of sowing rather than of harvest. By no means was "the crop assured," as Dr. Shattuck had said. And then the President brought to an end the centripetal thinking that was beginning to bind the imagination of the doctors:

> We want an opportunity to have clinics with all the hospitals in the city. We are calling men from other parts of the country as educators. We have two eminent ones here to-night. One is a professor of surgery and the other of medicine.

Mr. Lowell was referring to Dr. Cushing, who was to take up his work at the Peter Bent Brigham Hospital in the autumn, and to Dr. Edsall, already at the Massachusetts General Hospital and soon to become dean of the Medical Faculty.

President Lowell and Dean Edsall were not content merely to irrigate and till the the ground here at the head of Avenue Louis Pasteur, but turned their energies toward developing the educational and research potentials of the Massachusetts General and the Boston City hospitals as essential parts of the Harvard undertaking. These two leaders saw an accrual of strength to the University and an extension of Harvard's influence in the community and the nation through a dispersion of medical-school activities.

These references to some of the key figures must suffice as an indication of certain assumptions held by the planners and builders of the new School and by those who have charted its course. These assumptions can now be examined in more detail. Some were logical, and others nonlogical; each was in accord with the best evidence available at the time.

There was the underlying assumption that the practical art of medicine could be lifted out of the fog of medieval superstition by infusion of the methods of science; also, that the university was the most effective agency to undertake this task through the medium of education and the sponsorship of free inquiry. The stirring words of President Eliot, pro-

nouncing the final dedication of the new buildings on September 25, 1906, gave expression to this assumption; they activate our efforts today, and our faith in their validity can only be reaffirmed:

> I devote these buildings, and their successors in coming time, to the teaching of the medical and surgical arts which combat disease and death, alleviate injuries, and defend and assure private and public health; and to the pursuit of the biological and medical sciences, on which depends all progress in the medical and surgical arts and in preventive medicine.
>
> I solemnly dedicate them to the service of individual man and of human society, and invoke upon them the favor of men and the blessing of God.

It was the early recognition of the meaning of science to medicine, as expressed by these words of President Eliot, that placed the Harvard Medical School in the forward ranks along with Johns Hopkins, the University of Chicago and a few other institutions half a century ago. However, it is with respect to details that blueprints sometimes fail to express the full intent of the draftsmen. It may be of interest to turn from the major premise of the planners for a brief look at some of the plans and assumptions of a secondary order from the vantage point of half a century. In doing so, it is not the purpose to point out things that "need putting right." This is not even an attempt to identify "problems" as such. Rather, advantage is being taken of this backward glance to suggest lines of inquiry that may be useful as guidelines in long-term educational policy.

In 1906 there was almost complete acceptance of the idea that furtherance of the understanding of disease would be the product of research pursued in institutes of medical science. This concept was supported by a widespread adherence to the doctrine of specific etiology. Further, it was believed that such an institute could flourish in an isolated site — for example, in Manhattan along the East River or on a country estate in Boston beyond the Fenway. Proximity to a hospital co-operating with the medical faculty was desirable so that the students might walk the wards with a sympathetic instructor. Those engaged in clinical teaching would either "farm out" their research problems to the institutes of medical science or come to the quadrangle and pursue experiments on animals in a laboratory on some upper floor. Further, a finite number of so-called medical sciences were identified and established as the platform for the scientific development of medicine. Instruction in the same sciences was to underlie the strata of clinical studies. The medical sciences, some six or eight in number, were subdivisions of human biology representing the disciplines of the undergraduate curriculum. These in turn had been assembled in historical sequence as fields of learning proved useful to the healing art, starting in the fifteenth century with the dissection of the human body.

It is not necessary to review these several assumptions. Only a few happenings need be recalled to illustrate the great changes that have taken place in fifty years. For example, the emergence of the great teaching hospitals has brought many disturbing elements to the pastoral scene of 1906. These creatures are newcomers to our culture, contemporaries of the automobile, airplane and other noisy developments of this dynamic century. Hospitals of contemporary pattern, it must be remembered, became possible only in the closing decades of the nineteenth century when the passage of infection from one patient to another could be controlled by the simple technics of isolation.

Teaching hospitals are now playing an active and complementary part in medical education, and it is far from clear where the boundary line can be drawn between the functions of a university in professional education and those of a hospital. It can be questioned whether it is a responsibility of the university to teach the skills and information required for the practice of medicine. On the other hand, how far can a hospital go toward developing a general understanding of the mechanisms underlying the processes of health and disease and an understanding of the whole man? President Gilman, of Hopkins, tried to draw a sharp line in 1889 when he said: "All that belongs to medical instruction should be under the control of the University; all that belongs to the care of the sick and suffering . . . belongs to the Hospital."

Another example of the changes during fifty years merits consideration. These buildings were dedicated in 1906. The spring of 1908 saw the organization of the Society of Clinical Investigation, colloquially known as the Young Turks. In the following year the so-called "Meltzer Verein" — the American Society for the Advancement of Clinical Investigation — was founded. Unprecedented happenings began to take place in the hospitals. Instead of wearing the frock coat traditional to the morning rounds on the medical wards at the Massachusetts General Hospital, Dr. Edsall appeared in a surgeon's gown as if to show that to be a good physician one must be a surgeon as well, and use the hands to uncover knowledge. When the first ward for medical patients at the Peter Bent Brigham was opened on March 31, 1913, Francis W. Peabody was on hand as chief resident physician, sampling alveolar air with Walter Boothby. However, the story of the rise of clinical investigation in the hospitals does not need to be retold. The impact of this development on the whole field of medicine merits a deep and searching inquiry. In his first statement of policy as dean of the Medical School on April 7, 1919, Dr. Edsall deplored the trend, already evident, that a career in clinical investigation was attracting so many of the young men of scientific training and interest away from medical science as a profession. An inquiry on the impact of clinical investigation would thus lead to a consideration of what has been called the "plight of the medical

sciences." Here, the first question logically would be directed at establishing a definition. How does a medical science differ from any other or all other sciences? Is it merely that at one time it produced a golden egg of information useful to young physicians? Are not the medical sciences branches from large and dynamic areas of science held as captives within the medical faculty, where they must instruct students in the application of science to medicine? Is it reasonable to expect these branches to remain vigorous and productive and attract able recruits when splintered from their parent trunks? And again, while it has become fashionable for clinicians to press for even greater integration of their subjects with the medical sciences, is not their enthusiasm a bit like that of the cat desiring to integrate itself with the canary?

If the decision made in 1900 to place the School beyond the Fenway could be reconsidered today, it seems likely that the Faculty might elect to keep the hard core of science on which "depends all progress in the medical and surgical arts and in preventive medicine" closely within the circle of the general scientific activity of the University, even at risk of being submerged by the spring tides. After all, the School of Business Administration did not set up in State Street, nor did the Law School move to Pemberton Square!

Discussion

Although the Medical School took a significant step toward becoming the "great and ideal medical university" in 1906, it must be borne in mind that this was a directional movement toward a goal that can never be attained. This movement must be a continuous one. The medical faculty is rightly inarticulate when an attempt is made to define the purpose of its educational activities; there is such great and changing need for so many different kinds of doctors. Within six months of the time that ground was broken for this quadrangle in 1903, the Wright brothers succeeded in lifting their airplane off the ground at Kitty Hawk. Today, the human biologist is lagging far behind the physicist and engineer in the understanding necessary to the conquest of flight in the upper reaches of the atmosphere. Here is but a single example of the shortage of basically educated doctors of medicine whose analytical abilities and creative powers attract them toward the solution of unknown problems. This and similar areas of technology are closed books to the average medical graduate prepared to practice curative medicine.

The need is not for topflight scientists alone. It has become a platitude to voice the ambition to provide care for the *whole* man, knowing full well that it will take a *whole* doctor to care for the whole man. Today as never before the challenge of world needs for preventive medicine is extended to the medical graduate. So when a teacher or alumnus repeats that Harvard must select and educate *good* doctors, it can by no means be taken in the past sense of a pompous figure radiating optimism as he takes the pulse in a sickroom. Many different kinds of good doctors must be educated. A return must be made to Dr. Bowditch and his advice that medical education be adapted to the mind to be educated; to President Eliot, who showed us the limitations of the compulsory vocational curriculum; to President Lowell, who told us we treated a student as if he were a goose to be stuffed; and to President Conant, who wondered how much longer the Admissions Committee would give only lip service to the selection of "whole" men.

But it is not necessary to turn to the admonitions of the past. There can be no clearer guide today in a review of our educational policies than a sentence from still another Harvard President, Nathan M. Pusey: "The University's mission is to lead individuals with joy and understanding into an informed and thoughtful commitment to their lifetime enterprise within the common human adventure." Dedication to an ideal university medical school with this mission in mind will continue the production of good doctors, however varied their lifetime tasks may be.

The great undertaking of the Medical School as envisioned and built by President Eliot, J. Collins Warren and Henry P. Bowditch has served us well. During the past fifty years it has seen many changes. The opportunity for leadership in even greater change lies ahead if those who have followed after them show their courage to undertake the new activities that are in order. Change is but adjustment to the ebb and flow of human experience, and the success of the boldest plans will be assured when they unite the visions of youth with the dreams of age. Harvard must always look to the young men who may be building schools and laboratories in the air. For, as written by Archibald MacLeish:

> From the beginning of its history the next Harvard has been in process of evolution, and the next Harvard is in process of evolution now. Harvard, like other universities, is committed to one time and one time only — the future toward which the American Republic moves.

MEDICAL PROGRESS

GASTROENTEROLOGY*

SARA M. JORDAN, M.D.,† EVERETT D. KIEFER, M.D.,‡ S. ALLEN WILKINSON, M.D.,‡
FRANCIS E. McDONOUGH, M.D.,‡ JOHN R. ROSS, M.D.,‡ AND JOHN M. McGRATH, M.D.‡

BOSTON

THE subspecialty of gastroenterology continues to justify its existence as a medical entity not only because of the frequency and importance of diseases involving the digestive system but also because during the past three decades considerable progress has been made by specialists in the diagnosis and treatment of gastrointestinal disease. American gastroenterologists have been somewhat concerned with the relative paucity of investigative work in this field, but there is some current evidence that the experimental and investigative phase of gastroenterology will soon keep pace with clinical activity in this field. In November, 1955, a meeting of gastroenterologic investigators was held in Chicago to establish an informal group for the purpose of periodic discussion of research problems, and from this event it is hoped that co-ordination of effort and greater inspiration for new projects will develop.[1]

The present paper constitutes an attempt to survey recent progress in diseases of the gastrointestinal tract. Many interesting contributions cannot be included in this report because of space limitations, but by reference to papers of recent years we plan to indicate a trend in gastroenterologic endeavors and attainments.

ESOPHAGUS

In recent years both the normal function of the esophagus and the most commonly found dysfunction, cardiospasm, have been of interest to investigators. Butin et al.[2] showed, with the use of a miniature electromagnetic transducer, which recorded esophageal pressure after swallowing, that motility and appearance of positive pressures varied greatly and that in cardiospasm there was a consistent absence of a co-ordinated distally traveling peristaltic-type wave. Sleisenger, Steinberg and Almy[3] showed with studies of agents that stimulate or block the autonomic nervous system that excessive or unopposed sympathetic stimulation is not an important cause for failure of relaxation of the cardia. No new developments in therapy have been reported.

Esophagoscopy is rated by Brick and Palmer[4] as more effective than radiography in the diagnosis of esophageal varices. There seems to be unanimity of opinion favoring prompt utilization of the tamponade technic in checking massive hemorrhage from rupture of varices. A generally accepted sequence of procedures is hemostasis from varices before portavenous surgery. To determine the effectiveness of proposed portavenous shunt surgery, Browne and Welch[5] advocate hepatic catheterization, the reason for this recommendation being the finding of a direct ratio between hepatic-vein and venule pressures and direct portal-vein-pressure measurements during operation for portal hypertension.

Subacute erosive esophagitis has been identified by biopsy and has been differentiated from *esophageal peptic ulcer*,[6] a differential diagnosis that is important from the point of view of prognosis and therapy.

Cancer of the esophagus still presents great difficulties in diagnosis and treatment. Cytologic studies have been of help in effecting earlier and more accurate diagnosis and thus may help lengthen the present meager five-year survival rate with both surgical and supervoltage therapy.

The *cricopharyngeal diverticulum* is, in the experience of Lahey and Warren,[7] still thought to be best treated by the two-stage reparative procedure.

STOMACH AND DUODENUM

In the field of *gastric physiology* Scholer and Code[8] have conducted experiments with heavy water showing that water is absorbed into the blood stream from the stomach of healthy adults at a constant rate, and they suggest that this method can be utilized in determining the rate of absorption from other parts of the gastrointestinal tract. Owen, Bollman and Grindlay[9] have worked with a method for detecting hemorrhage from the gastrointestinal tract by using radiochromium-labeled erythrocytes. The much discussed problem of the relation of the gastric antrum to acid secretion and the development of peptic ulcer has been revived and again experimentally studied, as indicated by the report of Woodward et al.[10]

The *etiology of peptic ulcer* still remains indeterminate. The only recent concept has to do with the hormonal influence — the corticovisceral theory — described by Gray et al.[11] This concept has been expanded by other investigators and provides a fascinating new lead to this complex problem. Frumusan and Cattan[12] give some support to the general concept of hormonal influence by reporting 3 cases in which procaine infiltration of the communications between hypothalamus and prefrontal brain led to immediate relief of severe symptoms of peptic ulcer.

*From the Department of Gastroenterology, Lahey Clinic.
†Director, Department of Gastroenterology, Lahey Clinic.
‡Staff member, Department of Gastroenterology, Lahey Clinic.

In the *diagnosis of ulcer* radiologic study still holds its important place, and with technics of air-contrast and rugal-pattern studies, actual ulcer craters are visualized much more frequently than formerly. Because of possible confusion of actual with phantom craters, however, it is still highly important to make the diagnosis of ulcer from the clinical picture aided but not dominated by the x-ray findings. The place of gastroscopy with and without biopsy, even with its limitations of use, has attained established recognition as a means of diagnostic value. In this field the contributions of Benedict throughout recent years have been of special interest and importance. Cytologic studies have likewise assumed an important place in differentiation of benign from cancerous lesions.[13] Care in obtaining exfoliation of gastric mucosal and tumor cells, rapid delivery of these cells to a proper fixative before autolytic processes occur and the aid of a competent cytologist have been found essential for the success of this diagnostic measure.

Treatment of peptic ulcer is still generally regarded as ideally medical and surgical only when intractability of symptoms (usually due to penetration of the ulcer into an adjacent organ), obstruction due to cicatricial narrowing, perforation, uncontrollable tendency to hemorrhage, intractability of the patient under medical management or, in cases of gastric ulcer, a reasonable suspicion of malignant change is present. In a review of 1000 cases of gastric ulcer[14] slightly more than half the patients were operated upon because of intractability or suspicion that the lesion was malignant. Less than 10 per cent of the total group reviewed were found on histologic examination or by clinical course to have cancer.

Although discussions and even vehement debates still occur at medical meetings regarding the wisdom of surgical treatment of every gastric ulcer it is usually conceded that meticulously controlled medical trial management of gastric lesions that have the appearance of peptic ulcer is an accepted policy. There is increasing evidence in recent reports that the location of the gastric ulcer can no longer be considered significant in the differential diagnosis of malignant from benign lesions and that ulcers of the prepyloric area and greater curvature require the same discriminating tests as those of the lesser curvature and media. Surgery is acknowledged as more effective for gastric than for duodenal ulcer as far as incidence of stomal ulcer is concerned, but a certain percentage of difficult and at times intractable nutritional problems must be recognized as a possible postoperative complication.

In the *medical treatment* of peptic ulcer a large number of anticholinergic compounds have been developed in the past few years. These have shown a wide variability in individual response and reaction and in occasional unpleasant side effects. Furthermore, it has been observed clinically that healing of the ulcer may lag behind relief of symptoms. For all these reasons their use as a uniform and uncontrolled therapeutic measure has been discredited by many clinicians, and their usefulness limited to cases in which additional measures for temporary relief of otherwise intractable pain are required and strict surveillance of the patient is possible.

Massive hemorrhage from peptic ulcer is generally regarded as the most baffling complication both in the location of the site of bleeding and in the decision for or against immediate surgery. Earlier x-ray examination made with the utmost care is now more generally used, and surgery for the acutely and intractably bleeding ulcer has much less risk than formerly.

In *surgical treatment of ulcer* resection of the distal 70 per cent of the stomach is still regarded as affording excellent results. In certain special cases this operation or a resection of only half the stomach is combined by certain surgeons with vagotomy. The original combination of vagotomy with gastroenterostomy has given place to resection of varying extent with or without vagotomy.

Irradiation therapy to the body and fundus of the stomach for the primary purpose of producing a histamine achlorhydria, and by this means to control ulcer activity, has been used by Palmer et al.[15] in 1300 patients over a period of eighteen years for duodenal ulcer, and in only 1 case was carcinoma of the stomach found, and this in the antral portion. Approximately 5 per cent maintained a persistent histamine achlorhydria.

The effect of salicylates upon hypersensitive upper gastrointestinal tracts is now recognized, and Muir and Cossar[16] have reported the relation of salicylates with various solubility rates to the incidence of gastric hyperacidity and local peptic-ulcer formation.

Cancer of the stomach maintains its grim status as a most formidable and insidious disease. It is acknowledged that improvement in five-year survival rates after subtotal gastrectomy can be expected only through early diagnosis and perhaps increased scope of surgical extirpation. Mass screening tests for the detection of gastric cancer seem impractical. However, such tests appear indicated among known achlorhydric and hypochlorhydric patients, a group in which Hitchcock et al.,[17] in an extensive review, showed an increased incidence of gastric cancer.

Mosbech[18] has re-emphasized the relation of gastric cancer to pernicious anemia by reporting a large series in which, among relatives of patients with pernicious anemia, the incidence of gastric cancer was three times greater than that in a control group of similar age and sex distribution. For lymphoma of the stomach combined surgery and irradiation offer the best results.

In *surgery for gastric cancer* the controversy still continues concerning the relative merits of partial versus total gastrectomy. Statistical evaluation of longevity after surgical treatment of gastric cancer is

often unclear. Glass et al.[19] reported that after oral administration of cobalt^{60} and vitamin B_{12} patients who had had total gastrectomies showed no hepatic uptake of radioactivity whereas those who had had partial gastrectomies had a reduced uptake. Oral intake of intrinsic factor or parenteral administration of vitamin B_{12} produced a partial correction in this situation. Welbourn, Hallenbeck and Bollman[20] showed experimentally in dogs an excessive loss of fat absorption after gastric resections and emphasized the need for increased food intake in these cases.

Tumors of the duodenum with symptoms of ulcer-like pain, obstruction or hemorrhage have been infrequently reported and are usually diagnosed by x-ray study as discrete, often polypoid lesions in the proximal duodenum. They are usually aberrant pancreas, polyp or leiomyoma, and should always be removed if one is to avoid overlooking primary carcinoma. Becker[21] calls attention to cystic dilatation of Brunner's glands diagnosed radiologically by the presence of multiple radiolucent areas. This cystic hyperplasia is thought to be possibly due to a protective compensatory mechanism against gastric hypersecretion. In these cases surgical intervention is not indicated.

Small Intestine

Recent interest in small-bowel physiology and pathology has been focused to a large degree on the nutritional importance of this segment of the digestive tract and the diseases that interfere with this vital function.

That the small intestine plays a vital part in the absorptive process is a fundamental concept. In recent years there has been a gradual accumulation of data concerning the mechanism and role of specific areas of the small bowel in absorption.

Kremen and his co-workers[22] have shown experimentally the nutritional importance of the ileum by demonstrating that the ileum is the primary area of fat absorption in dogs. They found marked increases in fecal fat losses when segments of the distal small bowel were removed from intestinal continuity, whereas the proximal 50 to 70 per cent of the small intestine could be removed without ill effect. Their data suggest that protein absorption follows a similar pattern.

Working on human patients, Cummins and Jussila[23] found the absorption rates of 5 per cent and 10 per cent solutions of glucose to be respectively 29 per cent and 46 per cent less in the distal ileum than in the proximal jejunum. Figures of the same order of magnitude were found for the absorption of urea. Their data also suggest that water absorption may be decreased in the lower ileum. Present evidence suggests but does not prove that the intestine can increase its rate of glucose and methionine absorption under the influence of drugs that increase intestinal motility.[24] Evidence of malabsorption and the production of malnutrition in pathologic conditions of hyperperistalsis and surgical shortening of the small bowel are well known. Thus, to obtain optimal absorption there must be a high state of segmental activity without enough associated increase in peristaltic activity to move the absorbable material too rapidly away from the hyperabsorbing mucosa. The concentration of sodium chloride determines the absorptive rate of the solution, the more hypertonic solutions being absorbed to a significantly slower degree.[25] These data may be of some aid in the understanding of defects seen after gastrectomy with the gastrointestinal anastomosis in an area of reduced absorptive capacity.

It is well recognized that *sprue* is a deficiency state amenable to replacement therapy with liver extract, folic acid, folinic acid and vitamin B_{12} in addition to a high-protein, high-vitamin, low-fat diet. There is a consensus that tropical and nontropical sprue, idiopathic steatorrhea and celiac disease are varieties of the same disorder.[26,27]

The exact etiology of sprue is unknown. It is postulated that there is a primary selective defect in absorption. Cortisone and ACTH cause definite improvement, which can be maintained with these drugs. There is good evidence that these drugs improve the intestinal absorption of calcium, vitamin A, vitamin B_{12}, glucose, iron and fat.[28,29]

With the elimination of the glutin fraction of wheat and rye flour striking improvement has been noted in patients with celiac disease. Recently, subjective improvement, improvement of glucose and vitamin A absorption, and reversion of the radiographic appearance of the small bowel to normal have been reported in patients with sprue treated with this type of regimen.[30]

In the years since the original description of *intestinal lipodystrophy by Whipple,* there have been approximately 55 case reports in the literature. The condition is characterized by a "spruelike" diarrhea associated with rheumatic and serous-membrane manifestations. Arthritis, polyserositis and occasional endocarditis occur. The most characteristic lesions are collections of PAS (periodic acid-Schiff)-staining macrophages in the lymph nodes and the tunica propria of the mucosa of the small bowel. The material has been found to be a glycoprotein. Because of the rheumatic and serous-membrane manifestations of this disease, it has been considered a connective-tissue or collagen disease. No lesions typical of the rheumatic state, however, have been described in the small intestine, and the evidence points to an underlying and fundamental metabolic defect in the primary function of the intestinal mucosa[31] producing secondarily a polyserositis as a result of hypersensitivity to the mucoprotein substance. Previously, the diagnosis has been made by biopsy of the intestine or the mesenteric lymph nodes. Recently, the diagnosis has been established by biopsy of the peripheral

lymph nodes, adenopathy of this type occurring in about 50 per cent of cases.[32] Until the advent of steroid therapy Whipple's disease was considered a uniformly fatal condition. Recently, however, there are many case reports of successfully induced remissions with ACTH, cortisone and hydrocortisone.[31-33] There is suggestive evidence that hydrocortisone may be the most effective of these.[33]

Although *regional enteritis* was initially described in this country by Crohn more than two decades ago, the etiology still remains obscure. The pathologic process of progressive granulomatous lymphangitis, with secondary ulceration, cicatrization, fistula and abscess formation, has been described.[34] Recently, the extraileal pathological findings have been documented and found to be nonspecific.[35] A review of the classic clinical features and therapeutic programs has been included in the recent comprehensive study of Van Patter et al.[36] Of interest is a recent report of a case of incomplete infarction of the ileum simulating regional enteritis.[37]

The preoperative diagnosis of *small-bowel tumors* still remains a challenge. In one type of tumor, however, — carcinoid or argentaffinoma, — a syndrome is evolving that should lead to more accurate clinical diagnosis of this condition. The unusual clinical and pathological qualities of these tumors have served to attract interest out of all proportion to their incidence, for they comprise only about 1 per cent of all neoplasms of the gastrointestinal tract.[38] Most authors believe that all these tumors are potentially malignant but extremely slow growing. In various collective reviews 85 to 96 per cent have been located in the appendix, terminal ileum and cecum. Metastasis to the liver and regional lymph nodes occurs.

Carcinoid tumors, especially metastatic implants, have been found to contain large quantities of an indole derivative, 5-hydroxytryptamine (enteramine or serotonin), which is markedly vasoactive and has as one of its effects an elevation of pressure in the pulmonary artery.

In 1954 Thorson et al.[39] described an interesting syndrome of carcinoid of the small intestine with metastasis, generalized widening of the small vessels of the skin, plethoric coloration and total or partial cyanosis without polycythemia and pulmonary stenosis of the valvular type with tricuspid regurgitation. The valvular lesions differ morphologically and developmentally from other cases of pulmonary stenosis. The authors postulate that the secretion of serotonin over a long period gives rise to changes in the vascular bed that, if sustained, may result in organic alterations of the skin and, apparently, heart lesions.

In patients with carcinoid and cardiac abnormalities a hyperserotonemia and an increased urinary excretion of a serotonin metabolite, 5-hydroxyindoleacetic acid, have been demonstrated. From preliminary observations the urinary metabolite seems to be specific for metastatic carcinoid, but further evaluation seems advisable. A simple urinary test for 5-hydroxyindoleacetic acid has been described.[40] The use of this procedure and the knowledge of the secondary changes that carcinoid tumors may produce should lead to more frequent clinical diagnosis of this rare condition.

(*To be concluded*)

References

1. Editorial and proceedings of 1955 fall meeting of Gastroenterology Research Group. *Gastroenterology* (in press).
2. Butin, J. W., Olsen, A. M., Moersch, H. J., and Code, C. F. Study of esophageal pressures in normal persons and patients with cardiospasm. *Gastroenterology* **23**:278-293, 1953.
3. Sleisenger, M. H., Steinberg, H., and Almy, T. P. Disturbance of esophageal motility in cardiospasm: studies on autonomic stimulation and autonomic blockade of human esophagus, including cardia. *Gastroenterology* **25**:333-348, 1953.
4. Brick, I. B., and Palmer, E. D. Comparison of esophagoscopic and roentgenologic diagnosis of esophageal varices in cirrhosis of liver. *Am. J. Roentgenol.* **73**:387-389, 1955.
5. Browne, D. C., and Welch, G. E. Hepatic catheterization and upper gastrointestinal hemorrhage in portal hypertension. *J.A.M.A.* **158**:106-109, 1955.
6. Palmer, E. D. Subacute erosive ("peptic") esophagitis: clinical study of 100 cases. *Arch. Int. Med.* **94**:364-374, 1954.
7. Lahey, F. H., and Warren, K. W. Esophageal diverticula. *Surg., Gynec. & Obst.* **98**:1-28, 1954.
8. Scholer, J. F., and Code, C. F. Rate of absorption of water from stomach and small bowel of human beings. *Gastroenterology* **27**:565-577, 1954.
9. Owen, C. A., Bollman, J. L., and Grindlay, J. H. Radiochromium-labeled erythrocytes for detection of gastrointestinal hemorrhage. *J. Lab. & Clin. Med.* **44**:238-245, 1954.
10. Woodward, E. R., Lyon, E. S., Landor, J., and Dragstedt, L. R. Physiology of gastric antrum: experimental studies on isolated antrum pouches in dogs. *Gastroenterology* **27**:766-785, 1954.
11. Gray, S. J., Ramsey, G., Reifenstein, R. W., and Benson, J. A., Jr. Significance of hormonal factors in pathogenesis of peptic ulcer. *Gastroenterology* **25**:156-172, 1953.
12. Frumusan, P., and Cattan, R. Le problème de la maladie ulcéreuse. *Presse méd.* **63**:398-401, 1955.
13. Crozier, R. E., and Ross, J. R. Clinical application of gastric cytology studies. *New Eng. J. Med.* (in press).
14. Smith, F. H., Boles, R. S., Jr., and Jordan, S. M. Problem of gastric ulcer reviewed: study of 1000 cases. *J.A.M.A.* **153**:1505-1508, 1953.
15. Palmer, W. L., Kirsner, J. B., and Clayman, C. B. Cancer and radiation injury of stomach. *Gastroenterology* **30**:130-132, 1956.
16. Muir, A., and Cossar, I. A. Aspirin and ulcer. *Brit. M. J.* **2**:7-12, 1955.
17. Hitchcock, C. R., Sullivan, W. A., and Wangensteen, O. H. Value of achlorhydria as screening test for gastric cancer: 10-year report. *Gastroenterology* **29**:621-632, 1955.
18. Mosbech, J. Pernicious anemia and cancer of stomach: preliminary report. *Acta med. Scandinav.* **148**:309-315, 1954.
19. Glass, G. B. J., Mack, G. T., and Mersheimer, W. L. Uptake of radioactive vitamin B_{12} by liver in patients with total and subtotal gastrectomy. *Gastroenterology* **29**:666-683, 1955.
20. Welbourn, R. B., Hallenbeck, G. A., and Bollman, J. L. Effect of gastric operations on loss of fecal fat in dog. *Gastroenterology* **23**:441-451, 1953.
21. Becker, I. M. Cystic dilatation of Brunner's glands. *Gastroenterology* **27**:455-461, 1954.
22. Kremen, A. J., Linner, J. H., and Nelson, C. H. Experimental evaluation of nutritional importance of proximal and distal small intestine. *Ann. Surg.* **140**:439-448, 1954.
23. Cummins, A. J., and Jussila, R. Comparison of glucose absorption rates in upper and lower human small intestine. *Gastroenterology* **29**:982-992, 1955.
24. Cummins, A. J., and Almy, T. P. Studies on relationship between motility and absorption in human small intestine. *Gastroenterology* **23**:179-190, 1953.
25. Lee, P. R., Code, C. F., and Scholer, J. F. Influence of varying concentrations of sodium chloride on rate of absorption of water from stomach and small bowel of human beings. *Gastroenterology* **29**:1008-1016, 1955.
26. Rodriguez-Molina, R. Fundamental concepts in diagnosis of sprue. *Ann. Int. Med.* **40**:33-41, 1954.
27. Adlersberg, D., et al. Roentgenologic appearance of small intestine in sprue: long-term studies with special reference to differential diagnosis. *Gastroenterology* **26**:548-578, 1954.
28. Glass, G. B. J. Intestinal absorption and hepatic uptake of vitamin B_{12} in diseases of gastrointestinal tract. *Gastroenterology* **30**:37-52, 1956.
29. Mackay, I. R., and Volwiler, W. Effect of cortisone upon absorption of protein, fat, and calcium in idiopathic steatorrhea. *Gastroenterology* **28**:972-980, 1955.
30. Ruffin, J. M., Carter, D. D., Johnston, D. H., and Baylin, G. J. "Wheat-free" diet in treatment of sprue. *New Eng. J. Med.* **250**:281, 1954.
31. Jones, C. M., Benson, J. A., Jr., and Roque, A. L. Whipple's disease: report of case with special reference to histochemical studies of biopsy material and therapeutic results of corticosteroid therapy. *New Eng. J. Med.* **248**:665-670, 1953.
32. Puite, R. H., and Tesluk, H. Whipple's disease. *Am. J. Med.* **19**:383-400, 1955.

33. Wang, C. I., Janowitz, H. D., and Adlersberg, D. Intestinal lipodystrophy (Whipple's disease) amenable to corticosteroid therapy. *Gastroenterology* **30**:475-488, 1956.
34. Warren, S., and Sommers, S. C. Pathology of regional ileitis and ulcerative colitis. *J.A.M.A.* **154**:189-193, 1954.
35. Chapin, L. E., Scudamore, H. H., Baggenstoss, A. H., and Bargen, J. A. Regional enteritis: associated visceral changes. *Gastroenterology* **30**:404-415, 1956.
36. Van Patter, W. N., et al. Regional enteritis. *Gastroenterology* **26**:347-450, 1954.
37. Pope, C. H., and O'Neal, R. M. Incomplete infarction of ileum simulating regional enteritis. *J.A.M.A.* **161**:963, 1956.
38. DeLashmutt, R. E., and Kolozsi, W. A. Carcinoid tumors (argentaffinomas) of gastrointestinal tract: report of twelve cases. *Gastroenterology* **26**:743-753, 1954.
39. Thorson, A., Biörck, G., Björkman, G., and Waldenström, J. Malignant carcinoid of small intestine with metastases to liver, valvular disease of right side of heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and unusual type of cyanosis: clinical and pathologic syndrome. *Am. Heart J.* **47**:795-817, 1954.
40. Sjoerdsma, A., Weissbach, H., and Udenfriend, S. Simple test for diagnosis of metastatic carcinoid (argentaffinoma). *J.A.M.A.* **159**: 397, 1955.

MEDICAL INTELLIGENCE

CONTACT DERMATITIS FROM CHLORPROMAZINE HYDROCHLORIDE*

ROBERT F. TILLEY, M.D.†

BROOKLINE, MASSACHUSETTS

THE clinical applications of chlorpromazine hydrochloride have been the subject of extensive investigations. Among these are the control of nausea,[1] the management of manic states[2] and the relief of pain.[3] Undesirable reactions to the drug include postural hypotension, jaundice, local irritation at the site of injection and drug eruptions.

Recently, 8 patients were seen in whom a contact dermatitis followed exposure to chlorpromazine. These people were members of the nursing and household staffs of the Boston Lying-in Hospital. At this institution a study of chlorpromazine was started in December, 1953. The plan of the project required that the drug be injected by the nursing personnel of the delivery room. There were 21 nurses assigned to this department, exclusive of student nurses. The dermatitis developed in 5 of this group. A nurse and a maid responsible for cleaning the syringes were also seen with a similar picture. All had essentially the same dermatitis. The eruption first appeared on the hands and gradually spread to the arms, face and neck. The lesions were those of contact dermatitis — namely, edema, erythema, papules, vesicles, bullae, scales and fissures. Pruritus was present. Remissions followed absence from work for several days, and exacerbations occurred on re-exposure to the drug.

Patch tests to a variety of substances, including the chlorpromazine, were done. A stock ampoule of a 25 per cent solution of chlorpromazine was applied to a gauze bandage, and an occlusive dressing applied to the skin. This was kept in contact with the skin of the biceps area for seventy-two hours. At the end of this period the dressing was removed, and the area inspected. This inspection was repeated twenty-four and forty-eight hours later. The test was considered positive if erythema, edema and vesicles were observed at the site. After seventy-two hours positive reactions to the chlorpromazine were seen in the 8 patients.

The following case illustrates the clinical picture.

CASE REPORT

A 24-year-old graduate nurse was seen on June 8, 1954, complaining of a pruritic eruption of the hands and arms. During the previous 6 weeks she had noted the onset of a vesicular dermatitis on the right 2d and 3d fingers. This gradually involved the left hand and slowly spread over the forearms. Remissions were noted during absences of 2 or more days from the hospital. Recurrences followed return to work. Before the onset of her dermatitis she had been treated for urticaria in 1948, erythema multiforme in 1949 and chronic otitis externa during 1952 and 1953.

Physical examination showed an eruption involving the dorsal surfaces of the hands and forearms that was most severe on the right hand. There were edema, erythema, vesicles, serous exudation, scales and fissures. A diagnosis of contact dermatitis due to an agent employed at the hospital was established. A list of possible contactants was compiled. Topical therapy was prescribed, and the patient instructed to remain at home.

Subsequently, the eruption waxed and waned coincidentally with her presence at the hospital. The dermatitis eventually covered the exposed surfaces of the arms from the finger tips to the areas covered by the sleeves. One exacerbation followed a return to work of only 4 hours' duration. Various substances were handled by the patient. Repeated patch tests were done with these and other agents.

Finally, a patch test to chlorpromazine was applied. The material was obtained from a stock ampoule. After 72 hours the patch was removed, and a faintly erythematous reaction was noted. This reaction was more definite 24 hours later and persisted for 5 days. This test was done in July, and despite care and changes in assignments, the dermatitis continued until November.

DISCUSSION

In view of the extent of dermatitis, its severity and the number of persons in whom this sensitivity reaction developed, inquiries were made at several other hospitals employing chlorpromazine. No further cases were discovered. Tusques and Gambs[4] recently reported the occurrence of this problem in 35 persons employed in a mental hospital; all the patients were medical personnel, and all handled the solution form of chlorpromazine. Other reports[5-7] have empha-

*From the Boston Lying-in Hospital.

†Instructor in dermatology, Harvard Medical School; assistant dermatologist, Massachusetts General Hospital; consultant in dermatology, Boston Lying-in Hospital.

sized the severity of the contact dermatitis and Combes[8] pointed out the ease with which his patient became sensitized.

Through the co-operation of the Employee's Health Clinic patch testing with the stock solution of chlorpromazine was done in two groups of the staff of the Boston Lying-in Hospital. A total of 91 members of the nursing personnel were tested. Of these, 27 had positive reactions to the test. In another group of volunteers, composed of administrative personnel and members of the dietary group, no positive reactions developed. It seems, therefore, that the aqueous solution of chlorpromazine is a potent epidermal sensitizer, particularly in persons subjected to prolonged exposure.

Subsequently, in the last two years, with proper precautions the drug has not caused any unusual skin manifestations.

Summary

Chlorpromazine in solution was shown to be capable of producing a contact dermatitis in hospital personnel. The dermatitis was severe in 8 cases. All 8 patients had positive patch tests to the stock solution of chlorpromazine. Patch tests were positive in 27 cases out of 91 members of the nursing and housekeeping staffs. Thirty-four members of the administrative and dietary staffs had negative skin tests.

I am indebted to Florentino P. Pina, M.D., physician to the Employee's Health Clinic, and Miss Katherine C. Hough, R.N., for assistance in the procedure for the patch test.

References

1. Marks, J. H. Use of chlorpromazine in radiation sickness and nausea from other causes. *New Eng. J. Med.* **250**:999-1001, 1954.
2. Winkelman, N. W., Jr. Chlorpromazine in treatment of neuropsychiatric disorders. *J.A.M.A.* **155**:18-21, 1954.
3. Sadove, M. S., Levin, M. J., Rose, R. F., Schwartz, L., and Witt, F. W. Management of pain of malignant lesions. *J.A.M.A.* **155**:626-628, 1954.
4. Tusques, J., and Gambs, A. Accidents cutanés présentés par le personnel infirmier des hôpitaux psychiatriques manipulant la chlorpromazine (4.560 r.p. ou largactil, n.d.): leur prévention. *Ann. méd. psychol.* **112**:229-232, 1954.
5. Lewis, G. M., and Sawicky, H. H. Contact dermatitis from chlorpromazine: report of two cases. *J.A.M.A.* **157**:909-911, 1955.
6. Campbell, M. M. Chlorpromazine dermatitis. *J.A.M.A.* **159**:398, 1955.
7. Lewty, H. Dermatitis from chlorpromazine. *Pharm. J.* **175**:463, 1955.
8. Combes, F. C., and Reisch, M. Contact dermatitis due to chlorpromazine in dentist. *J.A.M.A.* **159**:807, 1955.

BY THE LONDON POST

A Lifelong Study — Musical Therapy — *Rock around the Clock*

JOHN LISTER, M.D.

LONDON

THE first World Conference on Medical Education gave an unprecedented stimulus to thought on the problem of how to turn out properly trained doctors. At the beginning of each new academic year, there are new thoughts on this old theme. As the mass of detailed scientific knowledge increases and the tendency toward ever-narrower specialization becomes more marked, so it becomes more apparent each year that the student must be taught to think and not to try to remember an increasing number of facts.

Professor Pickering, the recently appointed Regius Professor of Medicine at Oxford, believes that the problem lies in how to maintain the right balance between the two conflicting aspects of modern medicine — the technical and the professional. He believes that the best way of maintaining the correct balance is to ensure that the teaching of medicine remains within the sphere of the universities. In this country it is not necessary for the medical student to graduate in the arts or any other subject before beginning his preclinical studies. Because of this, it is vital that he should meet students of other faculties in his university days and so broaden his general outlook, which is in danger of being narrowed down so soon to a horizon bounded by a knowledge of electrolyte values, radioactive isotopes and electronics. Professor Pickering has said that the three great obstacles to a satisfactory medical education are its enormous content of so-called facts, its rigidity and its disorder. The growth of scientific knowledge has been accompanied by a corresponding growth in the content of the curriculum. But although much has been added, little has been taken away.

Professor Averill A. Liebow, of Yale, while visiting this country as prelector in the University of St. Andrews, gave an enlightened address in which he pleaded for medicine to be taught as human biology. The teacher, he said, should provide guidance, inspiration and opportunity. Given these, the student should be able to develop his own method of active scholarship. Furthermore, Professor Liebow said that the most important function of a medical school should be to ensure that such scholarship becomes for the doctor a lifelong activity. Indeed, it must do so because, medicine being a dynamic and not a static art, it is inevitable that much of what is taught to students today will be out of date tomorrow. It seems, therefore, a natural sequence that the second World Congress on Medical Education due in 1959 should be on postgraduate education, and it may well be that the central theme will be to present medicine as a lifelong study.

* * *

Noise continues to be one of the major characteristics of the age. The roar of traffic, the shriek of jet aircraft and the pneumatic drills are but a few of the insistent noises of the time. It is perhaps a reflection of this modern age of noise that a composer is reported to be writing, for a special occasion, a mi-

nor work scored for the vacuum cleaner. Perhaps he hopes to cheer the weary housewife by setting her favorite domestic machine to music, or perhaps he is one of the modern musicians who believe in the therapeutic value of music and thereby hope to induce a state of tranquillity into the domestic scene.

Certainly, music as a form of treatment is now being used in a number of centers. Although it is most beneficial in cases of mental illness, the teaching of music to spastic patients and long-stay patients with tuberculosis and even in geriatric units has been reported with success. Sick children are also being helped to recovery by music, and research workers in child-guidance clinics are trying to determine which music is the most suitable for each type of patient. Music of all kinds is being tried on the depressed children, those with schizophrenia and those with defective speech. Rhythm appears to be more important than the actual tune or melody, and the music is said to be more sedative in its effect than many of the latest tranquilizing drugs.

* * *

All this is in strange contrast with the uproars that have been started by the rock 'n' roll music of that provocative film *Rock around the Clock*. The film seems to have caused disturbances on both sides of the Atlantic, but its reception in England has apparently been more spectacular than that in America, where jazz and jive are more firmly rooted and where rock 'n' roll is perhaps only a further development.

In England the film has certainly set off a wave of hooliganism that has led many adolescents to the courts. Trouble has occurred both inside and outside the cinemas. When the film is being shown, it is often the signal for crowds of youngsters to begin to jive in the aisles while others throw missiles of all kinds from the galleries. After the offenders have been made to leave the cinemas they have continued their disorderly behavior in the streets, where many have come into conflict with the police. So serious have been the disturbances that many cinemas and local councils have had to ban the showing of the film.

The Teddy boy is said to be a strong influence in the rock 'n' roll riots although the truly sophisticated Teddy boy is said to despise this type of music and 6 chimpanzees from the Liverpool Zoo are reported to have given the film no more than mild applause. Why should these creatures from the jungle be so unmoved by this music, which has set teen agers jiving? Sir Malcolm Sargent, the chief conductor of the B.B.C. Symphony Orchestra, has probably given the answer. He has said that the current craze is nothing more than an exhibition of primitive tom-tom thumping. He could not understand why so many youngsters could sincerely believe there was anything weird or wonderful about the music that has been played in the jungle for centuries. No wonder the chimpanzees were bored!

The *Times* believes that much of the present hooliganism has drawn strength from an atmosphere such as that which surrounds undergraduate college rags. It suggests that too much can be made of the recent incidents, and without excusing them, recommends that young people who behave like hooligans should not be paid the compliment of being analyzed as sinister developments in mass behavior. The *Observer* sees the jiving craze as a symptom of a frustrated impulse to do something vigorous and exciting, and suggests that it has possibly more promise than the ballroom perambulations of the thirties. Bashing policemen and breaking up cinemas can have nobody's sympathy, but rather than deplore rock 'n' roll, it is suggested that it would be better to give these pent-up energies some constructive outlets without taming them.

BRIEF RECORDING

Mumps and Presternal Edema

Lewis E. Braverman, M.D.,* and Isadore Gershman, M.D.†

Boston

SINCE the first description of a nontender presternal swelling associated with epidemic parotitis in 1918[1] few references to this phenomenon have appeared in the medical literature.[2-4] Its occurrence in large epidemics in the armed forces has been variously placed between 1 and 6 per cent.[5-8] It is a benign complication of mumps, and should be recognized as such. The following case report is illustrative of the clinical course of this entity.

Case Report

R.L. (C.V.C.H., 95182), a 4½-year-old boy, first entered the hospital because of a nonpainful swelling over the upper sternum of 12 hours' duration. Seven days previously he had general malaise, slight fever and a sore throat. Two days later his family physician was consulted because of bilateral parotid and anterior cervical swelling; a diagnosis of mumps, with involvement of the parotid and submaxillary glands, was made. The course of the disease was benign.

On the morning of admission the patient's mother noted a swelling over the upper sternum. The patient felt well and was afebrile.

Physical examination revealed a husky boy who appeared well. The vital signs were normal. The only positive physical findings were pronounced fullness of the submaxillary and parotid glands and a subcutaneous, soft, slightly pitting, nonfluctuant, nonerythematous, nontender, noncrunching, ill defined swelling over the manubrium and surrounding area. The hospital course was benign, and

*Formerly, intern in internal medicine, Beth Israel Hospital.
†Visiting pediatrician, Rhode Island and Charles V. Chapin hospitals, Providence, Rhode Island.

the presternal edema completely subsided within 36 hours of admission. The submaxillary and parotid swelling also diminished markedly within this 36-hour period. X-ray

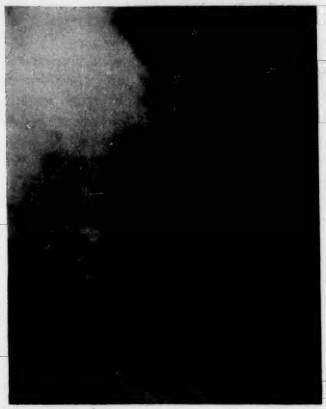


FIGURE 1. *Roentgenogram Taken on Admission (Note the Presternal Edema).*

examinations on admission and discharge (Fig. 1 and 2) showed the presternal edema and its disappearance.

lymphatic drainage of the upper sternal area. The swelling of the submaxillary glands and surrounding tissue impedes the flow of lymph at the level of the deep cervical lymph nodes, which receive afferents from the superficial lymphatic vessels of the upper anterior thorax. This results in stasis and subsequent lymphedema of the presternal area. The presternal edema may therefore be seen in any condition that leads to severe swelling in the anterior cervical area. It is also seen when the subcutaneous lymph drainage of the anterior chest wall to the deeper subpleural and intermuscular vessels is blocked by sternal and retrosternal involvement in malignant lymphoma.[9]

CONCLUSIONS

Presternal edema is a benign manifestation of epidemic parotitis. It may, however, be seen in more serious conditions, leading to lymph stasis in the presternal area.

REFERENCES

1. Radin, M. J. Epidemic of mumps at Camp Wheeler, October, 1917–March, 1918. *Arch. Int. Med.* **22**:354-369, 1918.
2. Barker, C. S. Complication of mumps — swelling over manubrium sterni. *Canad. M. A. J.* **48**:22, 1943.
3. Rappaport, J. N. Mumps with edema of chest. *Illinois M. J.* **83**:133, 1943.
4. Walker, J. S., and Gann, E. L. Laryngeal edema in epidemic parotitis. *Ann. Otol., Rhin. & Laryng.* **57**:163-166, 1948.
5. Gellis, S. S., and Peters, M. Mumps with pre-sternal edema. *Bull. Johns Hopkins Hosp.* **75**:241-250, 1944.

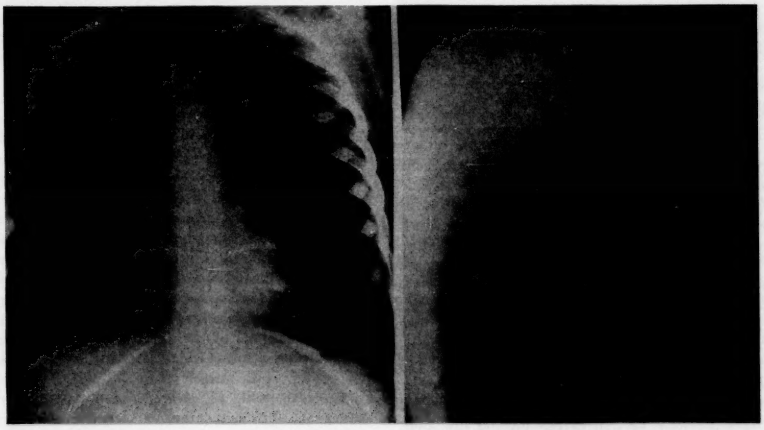


FIGURE 2. *Roentgenograms on Discharge — the Edema Has Completely Disappeared.*

DISCUSSION

In the majority of the reported cases there was severe submaxillary-gland swelling. The probable cause of the presternal edema is blockage of the

6. Haerem, A. T. Observations on mumps in soldiers. *Mil. Surgeon* **97**:33-39, 1945.
7. Eagles, A. Y. Analysis of 4-year epidemic of mumps. *Arch. Int. Med.* **80**:374-387, 1947.
8. Warren, W. R. Some observations on mumps. *Mil. Med.* **118**:23-30, 1956.
9. Fleischner, F. G., Bernstein, C., and Levine, B. E. Retrosternal infiltration in malignant lymphoma. *Radiology* **51**:350-357, 1948.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42481

PRESENTATION OF CASE

A seventy-four-year-old widow entered the hospital because of a radiologic abnormality noted in the region of the right kidney.

Sixteen months previously she was admitted to another hospital because of episodes of painless hematuria that occurred over a period of one week. An intravenous pyelogram was said to have demonstrated a lesion in the upper pole of the right kidney and blood clots in the renal pelvis (Fig. 1*A* and *B*). She failed to keep subsequent appointments. There were no further episodes of hematuria, and she remained well. Three months before admission an intravenous pyelogram demonstrated a spherical defect, 2 cm. in diameter, that displaced the superior calyx of the right kidney anteriorly and laterally; the lower portion of the defect was calcified; no other abnormalities were noted in either calyceal system. The ureters and urinary bladder were normal. Severe degenerative changes were noted in the lumbar spine, with narrowing of the interspace between the fourth and fifth lumbar vertebras. A retrograde pyelogram two months later showed no change in the appearance of the right kidney; the calcification in the region of the upper major calyx was still present (Fig. 2). Cytologic examination of the urine from the right kidney for malignant cells was unsatisfactory. Films of the chest demonstrated moderate enlargement of the heart in the region of the left ventricle. X-ray films of the skull and thoracic and lumbar spine were normal except for the previously noted degenerative changes and bony bridges anteriorly around some of the mid-thoracic intercostal spaces. The urine gave a + test for albumin; the sediment contained occasional red cells and 75 white cells per high-power field.

Physical examination revealed a well nourished, husky woman. The heart was questionably enlarged. A Grade 2 precordial systolic murmur that was best heard in the aortic area was audible. The abdomen was obese. No masses were palpable.

The temperature was 98.6°F., the pulse 92, and the respirations 16. The blood pressure was 190 systolic, 90 diastolic.

The urine gave a ++ test for albumin; the sediment contained 50 red cells and 10 white cells per high-power field; a culture showed no growth. Examination of the blood revealed a hemoglobin of 14.4 gm. per 100 ml. and a white-cell count of 11,100. The nonprotein nitrogen was 26 mg., the calcium 9.1 mg., the phosphorus 3.4 mg., and the fasting blood sugar 110 mg. per 100 ml. The alkaline phosphatase was 4.3 and 2.5 units. An electrocardiogram showed mild nonspecific ST-segment and T-wave changes compatible with coronary-artery disease. Cytologic examinations of the urine for malignant cells were doubtful and negative.

An operation was performed on the third hospital day.

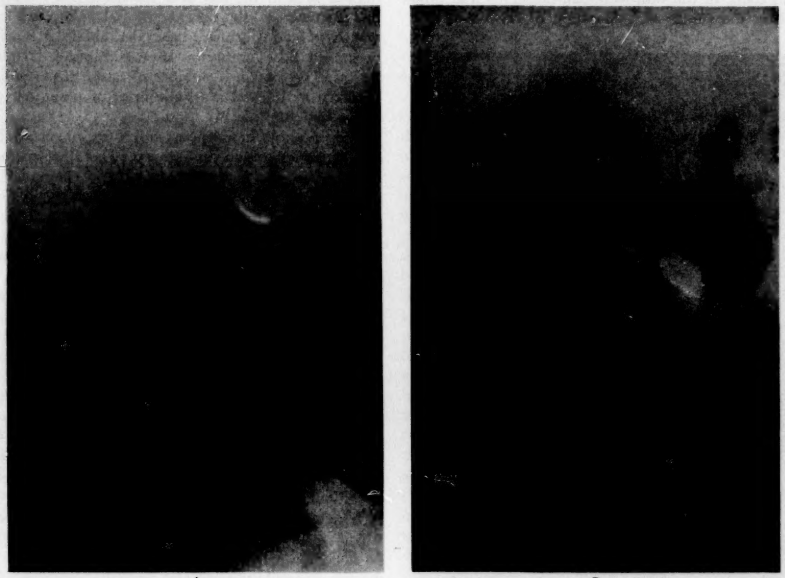
DIFFERENTIAL DIAGNOSIS

DR. JOSEPH HANELIN*: This case lends itself well to a radiologic discussion. We are primarily interested in the nature of the renal lesion on the right, which caused a single episode of hematuria sixteen months previously and which was probably responsible for the microscopic hematuria at the time of admission. The patient was asymptomatic and had as "chief complaint" only an abnormality in the x-ray film. Three days after admission an operation, probably a nephrectomy on the right, was done. The laboratory data, aside from the hematuria, are not helpful although not misleading. The albumin in the urine was probably related to the moderate hypertension in an elderly patient, who also had evidence of hypertensive and coronary-artery disease. The cytologic examinations of the urine were inconclusive. The slightly elevated white-cell count I shall disregard. The physical examination was normal except for the elevated blood pressure and the systolic murmur.

The chief interest centers about the x-ray examinations. In these films from the examination done in another hospital sixteen months before the surgical procedure, there is an arcuate band of calcification in the upper pole of the right kidney that partially circumscribes a mass, which is about 2 cm. in diameter. A few punctate densities lie above the curvilinear streak itself (Fig. 1*A*). The intravenous pyelogram shows the calcification in relation to the superior infundibulum along its medial aspect, gently indenting the infundibulum and depressing it somewhat laterally and in an anterior direction as seen in an oblique film (Fig. 1*B*). There are multiple filling defects within the renal pelvis and calyxes that are probably caused by blood clots. They are not visible

*Associate radiologist, Massachusetts General Hospital.

in later pyelograms. In a retrograde study the calcification is again noted in the same position and is again very gently impressing the medial aspect of the superior infundibulum (Fig. 2).



A B

FIGURE 1. *Roentgenograms Taken Sixteen Months before Admission. In the plain film of the right kidney* (A) *there is an arcuate calcification in the right upper pole (arrow). The intravenous pyelogram* (B) *shows the calcification pressing upon the medial aspect of the superior major infundibulum (arrows). There are filling defects of the renal pelvis produced by blood clots.*

There is nothing unique about hematuria occurring with a small lesion in the kidney, but there is something of particular interest in the fact that the lesion is distinctively calcified. Its completely intrarenal location is incontrovertibly established by multiple projections. I shall have to consider briefly the major diseases that can involve the kidney, among which are primary renal neoplasms. It is rare, indeed, to see this type of calcification in a renal neoplasm, particularly in one of small size; that is the chief reason for excluding it. A simple cyst, particularly one of small size, does not ordinarily contain calcification of this extent in its wall, nor does an echinococcus cyst. Generally, they have attained considerable size before calcification develops. Renal calculi may show this particular type of calcification at times, but when they are of this size and configuration they are almost invariably present within a calyx — often a dilated minor calyx. This was external to both the minor and major calyxes. A calcified tuberculous or nonspecific infectious lesion rarely exhibits the annular deposition of calcium seen in the present case.

I am led to the one possibility that seems to be the best explanation for this particular shadow — that is, an aneurysm of a branch of the renal artery. This is an extraordinarily rare lesion and even more rarely occurs in this particular location (intrarenally) so that one is hesitant to mention it, but nothing else seems to fit quite as well. The gross appearance of the lesion, if it were not in the kidneys, would not disturb me because it looks typically like any aneurysm with a calcified wall.

A number of reviews of this subject have been published over the years[1-3]; in 1951 Abeshouse[4] reported upon 115 cases in the literature and added 2 of his own, and I am indebted to him for the following statistical information. The rarity is impressive when one considers that in 100,421 autopsies from seven different sources, there were only 1340 aneurysms of all kinds and only 12 (or 1 in 8400) involved the renal artery. They may be found at any period of life, from one year of age into the eighties; most of them were in patients in the fifth and sixth decades. They occurred in about equal numbers in both sexes and

in both the right and the left kidney. There is a true and a false type of aneurysm of the renal artery. The lesion in the patient under discussion was probably a true aneurysm, for I suspect that a portion, or several coats, of the wall were still preserved and intact within the aneurysmal dilatation of the vessel.

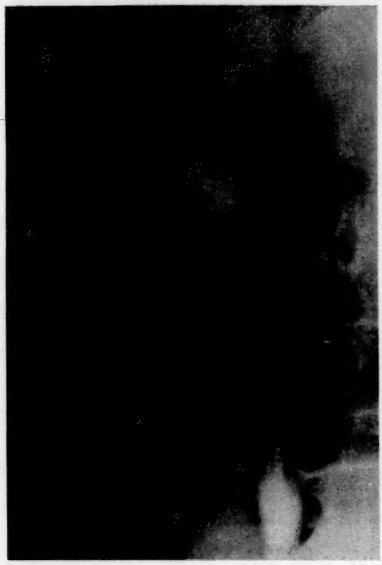


FIGURE 2. *Right Retrograde Pyelogram.*
The deformity of the superior infundibulum is present. Note the disappearance of the filling defects of the renal pelvis.

The etiology has been open to much discussion. It may be congenital according to some authorities; indeed, some have compared it to the intracranial aneurysm. An aneurysm might be acquired on a degenerative, an inflammatory or a traumatic basis, and may be saccular or fusiform but is more likely to be saccular. Dissecting aneurysm of the renal artery is exceedingly rare, unless it is in contiguity with a dissection of the aorta itself. The arteriovenous aneurysm is particularly unusual.

The precise location of the aneurysm most commonly is medial to the bulk of the renal shadow, overshadowing the renal pelvis or slightly medial to it. In the cases in which the site was indicated in the literature, 66 were in the main renal artery before it branches, 31 in the main branch, which usually divides into 3 and occasionally into 5 vessels, and 10 in an intrarenal or intralobular artery. If the lesion under discussion was an aneurysm, it probably developed from an intralobular vessel, perhaps at its junction with a branch of the main artery. In 5 cases there was more than 1 aneurysm in the kidney.

The true aneurysm is often totally asymptomatic. Sixty-three patients, however, had pain, either in the lumbar area or directly over the aneurysm itself; 41 had hematuria, and 31 had a palpable mass, the aneurysm having grown to considerable size or having become a false aneurysm through rupture. Tenderness was present in a number of cases; hypertension occurred in 19, and a systolic bruit or pulsation was recognized in 12.

Very few of these aneurysms were diagnosed before either operation or autopsy. The chief method of diagnosis was by radiography. The characteristic shadow is the ringlike calcification that the patient under discussion presented. Abeshouse,[4] in his review, reported the first case found by arteriography, which was done by the retrograde route through the femoral and iliac arteries and aorta with direct injection of the radiopaque medium into the orifice of the renal artery. Abdominal aortography also could be utilized to demonstrate such a lesion. Another method that might be employed is called nephrotomography, which utilizes the planigram or laminagram, together with very rapid injections of contrast substance, after which films are immediately taken. Such films will demonstrate a diffuse blush in the kidneys caused by capillary filling and may even at times reveal some of the major arterial vessels. That might have been an aid in this particular case.

Why was this woman subjected to a nephrectomy? I assume it was because of the continued bleeding. I do not know whether an aneurysm was suspected at the time; possibly, carcinoma was the diagnosis. In any event it may have been a wise course, even though the patient was seventy-four years old, because the prognosis with the symptomatic aneurysm is poor. I think at least 30 per cent of the patients described in the literature who were not operated upon died.

DR. BENJAMIN CASTLEMAN: The official radiologic report was that this was a cyst with a calcified wall, or possible hypernephroma. Can you rule out a cyst with a calcified wall?

DR. HANELIN: I have never seen one of this size that had a calcified wall. Moreover, the thickness of the calcification would be unusual even for the average cyst of a large size. I have not seen a small carcinoma of the kidney calcify in this fashion. Calcification in renal carcinomas generally occurs when they attain large size and become necrotic.

A PHYSICIAN: Could this have been a hematoma with calcification?

DR. HANELIN: I have never seen a hematoma of the kidney result in this type of calcification.

DR. VICTOR A. POLITANO: I have seen signet-ring or peripheral calcification in both cysts and tumors; although they usually are larger, they can occur in a lesion of this size. I think that Dr. Colby might comment on this.

DR. FLETCHER S. COLBY: I think that Dr. Hanelin has covered the data well. It seems to me that the x-ray appearance suggests a definite mass that deforms the upper calyxes of this kidney. My experience with intrarenal aneurysm is nil, but they are such rare birds that on the theory of chances I should expect a tumor mass with calcium in it, most likely a renal-cell carcinoma.

A PHYSICIAN: Dr. Hanelin, could an angioma calcify in this manner?

DR. HANELIN: I have never seen an angioma of the kidney calcify. If one were to do so, I should anticipate multiple annular shadows of smaller size, or possibly multiple phleboliths.

CLINICAL DIAGNOSIS

Carcinoma of kidney.

DR. JOSEPH HANELIN'S DIAGNOSIS

Arteriosclerotic aneurysm of branch of renal artery.

ANATOMICAL DIAGNOSIS

Arteriosclerotic aneurysm of branch of renal artery.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Were you at the operation, Dr. Politano?

DR. POLITANO: I was not at the operation, but I know what was found. The surgeons found exactly what Dr. Hanelin has described. This was an aneurysm of a branch of the renal artery. The possibility of an aneurysm was discussed when they looked at the x-ray films, but as Dr. Hanelin and Dr. Colby pointed out, this is so rare that it was not considered seriously. Also, the film does suggest a space-filling mass in the upper pole of the kidney, so an aneurysm seemed less likely.

DR. CASTLEMAN: The aneurysm was filled with a thrombus. This was an arteriosclerotic aneurysm of the renal artery — not a false one but a true one — similar to the aneurysm that we see in the splenic artery or other large arteries. One can understand how this could press on the epithelium of the calyxes and produce hematuria.

DR. POLITANO: About the treatment of this particular case, most patients with aneurysms of the renal arteries who have not been operated upon have died within two years after the diagnosis has been made. The proper treatment, of course, is nephrectomy; or perhaps nowadays we might consider an arterial graft.

DR. HANELIN: Would a heminephrectomy be a possibility in a case like this?

DR. POLITANO: Yes; that might be considered in this patient because of the location of the lesion.

REFERENCES

1. Mathé, C. P. Aneurysm of renal artery. *J. Urol.* **27**:607-636, 1932.
2. Lowsley, O. S., and Cannon, E. M. Aneurysm of renal artery: report of case. *J.A.M.A.* **121**:1137-1143, 1943.
3. Silvis, R. S., Hughes, W. F., and Holmes, F. H. Aneurysm of renal artery. *Am. J. Surg.* **91**:339-343, 1956.
4. Abeshouse, B. S. Aneurysm of renal artery: report of 2 cases and review of literature. *Urol. & Cutan. Rev.* **55**:451-463, 1951.

CASE 42482

PRESENTATION OF CASE

A seventy-year-old man entered the hospital because of shortness of breath.

Seventeen years previously he noted occasional brief episodes of wheezing and exertional dyspnea that were unrelated to the time of year or known allergens. Two years before entry he was admitted to another hospital for three weeks because of status asthmaticus. He was digitalized. Subsequently, there was edema of the ankles that subsided. Because of gradually increasing fatigue, weakness and exertional dyspnea he stopped working about fourteen months before admission. X-ray films of the chest a year before entry were said to have demonstrated an enlarged heart, increased bronchovascular markings and pulmonary emphysema. The hematocrit, which was 65 per cent at this time, fell to 49 per cent after three venesections. Clubbing of the fingers was thought to have been present for no longer than a year before admission. In the year before entry Meticorten and occasionally ACTH had been given for acute asthmatic attacks. During this time there were three episodes of tachycardia that were relieved with quinidine therapy. Three months before admission the edema of the ankles recurred, and the weakness increased until he was unable to move more than a few steps or to lift his arms. Moist pulmonary rales that subsided with diuretic therapy were audible. During the week before admission orthopnea was noted for the first time, and on the day of entry there was a severe attack of wheezing. There was a loss of 26 pounds in weight during the two years before admission.

Physical examination showed a cyanotic, dyspneic man of asthmatic physique. There was no distention of the veins of the neck. No lymphadenopathy was present. Examination of the chest revealed slight widening of the mediastinum and a slight increase in the anteroposterior diameter. There was dullness to percussion, with diminished breath sounds, over the lower half of the left side of the chest and over the left apex posteriorly. Wheezes throughout both lung fields, with prolonged expirations, were noted. A few moist rales were audible at the right-lung base. Examination of the heart revealed a normal sinus rhythm at a rate of 120. No murmurs were heard. The abdomen was normal. There was + + pitting edema of the legs. Clubbing of the extremities was present. Arterial pulses distal to the femoral pulse were absent bilaterally.

The temperature was 101.6°F., the pulse 120, and the respirations 30. The blood pressure was 120 systolic, 70 diastolic.

The urine gave a + + test for albumin; the sedi-

ment contained 2 to 5 white cells and an occasional hyaline cast per high-power field. Examination of the blood revealed a hemoglobin of 15.2 gm. per 100 ml., a hematocrit of 49 per cent and a white-cell count of 23,200, with 93 per cent neutrophils. The nonprotein nitrogen was 62 mg., the total protein 5.7 gm., the albumin 3.1 gm., and the globulin 2.6 gm. per 100 ml. The sodium was 129 milliequiv., the potassium 4.9 milliequiv., the chloride 82 milliequiv., and the carbon dioxide 37 milliequiv. per liter. The arterial oxygen content was 11.9 vol. (normal, 15-23 vol.), the oxygen capacity 18.7 vol. per 100 ml., and the oxygen saturation 63 per cent (normal, 96-100 per cent). The arterial carbon dioxide was 33 milliequiv. per liter; the partial pressure of the carbon dioxide was equivalent to 43 mm. of mercury. The serum pH was 7.43. Cultures of the sputum and the throat grew out abundant alpha-hemolytic streptococci and a few nonhemolytic streptococci. Cultures of the blood showed no growth. X-ray films of the chest demonstrated a left-sided hydrothorax that obscured the left-lower-lung field and cardiac silhouette; the left upper lung was clear; the right lung showed coarse bronchovascular markings; the right leaf of the diaphragm was low and flattened. An electrocardiogram showed a sinus tachycardia at a rate of 115; the PR and QRS intervals were 0.14 and 0.06 seconds respectively; Q waves were present in Leads V_1 through V_3; there was sagging of the ST segments in Leads 1, 2, 3, aVL and aVF; there was slight elevation of the ST segments with terminal inversion of the T waves in Leads V_1, V_2 and V_3; the ST segments were depressed in Leads V_5 and V_6.

With antispasmodic therapy the wheezing subsided, but the patient became progressively more cyanotic and the blood pressure rose to 260 systolic. With oxygen therapy the blood pressure fell to normal, and the cyanosis was relieved. A thoracentesis on the left yielded 1000 ml. of cloudy, yellow fluid that contained 2600 white cells per cubic millimeter, with 39 per cent neutrophils, 55 per cent lymphocytes and 6 per cent monocytes; the specific gravity was 1.012, and the total protein 2 gm. per 100 ml. Subsequently, a coarse pleuropericardial friction rub was audible over the cardiac apex. This was heard for several days and then disappeared. On the second hospital day an irregular cardiac rhythm at a rate of 150 was noted. Physical examination showed no change, except that there was no longer peripheral edema. The blood pressure was normal. An electrocardiogram showed a supraventricular tachycardia with a wandering pacemaker that was suggestive of atrial fibrillation in some leads. After 0.25 mg. of Digoxin, in addition to the maintenance dosage of digitalis, the pulse rate fell from 160 to 120 in several hours. On the next day electrocardiograms showed atrial fibrillation with a ventricular rate of 136. On the fourth hospital day the pulse rate fell from 120 to 108 and became regular after quinidine lactate given intramuscularly. A Grade 2 systolic murmur was heard along the left sternal border. An electrocardiogram showed reversion to a normal sinus rhythm. With quinidine and digitalis the cardiac rate remained regular between 88 and 108 during the next two days. During this time the patient became increasingly drowsy. Physical examination showed no change. The temperature ranged between normal and 100°F. On the seventh hospital day a tachycardia at a rate of 186 was noted. An electrocardiogram showed atrial fibrillation. After 0.2 mg. of Cedilanid the cardiac rate fell to 140 and was regular. On the next day x-ray films of the chest (Fig. 1) demonstrated considerable improvement in the appearance of the left side of the thorax; the left leaf of the diaphragm still appeared somewhat elevated; the homogeneous density obscuring the left border of the heart was still seen; there appeared to be some compensatory emphysema in the lower lobe and the aerated portions of the left upper lobe; the right lung showed considerable diffuse fibrosis and appeared to be overaerated; the right leaf of the diaphragm was considerably

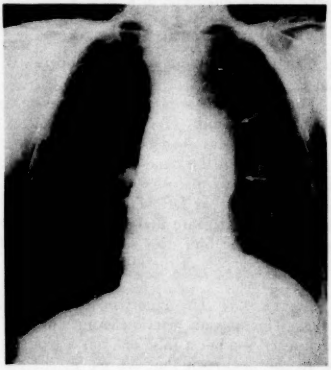


FIGURE 1. *Posteroanterior Roentgenogram of the Chest. The left leaf of the diaphragm is elevated. There is a density (arrows) adjacent to the left aspect of the mediastinum caused by a completely collapsed left upper lobe.*

flattened. An electrocardiogram showed atrial fibrillation but Lead V_3R demonstrated regular atrial activity at a rate of 140 with a regular ventricular response and first-degree heart block for several beats and then a run with a variable PR interval and an occasional loss of a ventricular response; the ventricular response was normal in configuration. Several hours later physical examination showed no change. The veins of the neck were not distended when the patient was elevated to an angle of 30°. The pulse was 120, and the blood pressure 80 systolic, 50 diastolic. The white-cell count was 27,700. An electrocardiogram showed no significant changes. Subse-

quently, the cardiac rate gradually rose to 142 in spite of Cedilanid given intramuscularly. He was found dead early the next day.

Differential Diagnosis

Dr. Kenneth T. Bird*: This elderly man appears to have had progressive pulmonary and cardiac failure, which became most apparent at the age of sixty-eight years. Despite digitalization he was forced into retirement fourteen months before the final illness. Shortly after this, an x-ray film of the chest showed cardiac enlargement with increased bronchovascular markings.

At the time of the film of the chest taken a year before admission the patient was found to have a polycythemia assumed to be secondary to the pulmonary emphysema, since it was treated by venesection. He was also noted to have clubbing of the fingers, apparently of recent onset. This could well have been the first clue to the presence of underlying neoplasm of the lung, or it may merely have been indicative of the known chronic disease of the lungs, with or without anoxemia. I shall exclude the other known extrapulmonary causes of hypertrophic osteoarthropathy. Clubbing that is acute in onset and associated with pulmonary neoplasm is often painful. Unless the clubbing is painful it is very difficult to date the onset of the condition. The vast majority of patients with clubbing recognize its presence only after it is called specifically to their attention.

In the year before the final hospitalization, both pulmonary and cardiac complaints fluctuated and culminated in persistent edema of the ankles three months before admission. The heart failure had recurred. The marked weakness described during this period may have been caused by vigorous diuresis with the development of hyponatremia, hypochloremia and alkalosis, which was found to be present on admission. It would be of interest to know whether the patient had been on a low-sodium diet during this period.

One week before admission orthopnea developed, and severe wheezing occurred several days later and led to hospitalization. In view of the electrocardiographic findings, myocardial infarction, probably septal, best accounts for this development. Serial tracings would help to decide that. Because of the fever and elevated white-cell count, an associated acute pulmonary infection must be considered. An acute pulmonary infection is one of the commonest precipitating causes of heart failure — either right-sided or left-sided. Incidentally, the insidious weight loss of 26 pounds during the two years before admission may have been the result of the chronic anorexia of heart failure with its resultant poor nutrition or associated with anoxia or even with the cachexia of neoplasm.

Physical examination suggested pulmonary emphysema, which had not led to carbon dioxide retention, for there was a normal partial pressure of carbon dioxide in the arterial blood. The patient had marked anoxia with an arterial oxygen saturation of only 63 per cent. Since the determination was made while he was in cardiac failure, no particular significance can be attached to this finding because anoxia is the rule in cardiac failure. I shall only wonder about an alveolar-capillary-block syndrome. There was ++ pitting edema of the ankles, but the liver was not felt.

The albuminuria and elevated nonprotein nitrogen are consistent with congestive heart failure whereas the hypoalbuminemia suggests poor nutrition.

In an attempt to give an etiologic diagnosis and to correlate the pulmonary and cardiac findings, the chest films may be helpful. May we see the films, Dr. Hanelin?

Dr. Joseph Hanelin: There are chest films taken a week apart, the last examination a day before death. Initially, fluid in the pleural space obscures the lower third of the left-lung field. There is in addition a homogeneous density lying adjacent to the mediastinum from the level of the aortic arch to the inferior cardiac margin. Subsequently, in the films taken a week later, the mediastinal area is better shown when the fluid has largely disappeared. It is evident at this time that the density adjacent to the heart and great vessels represents a completely collapsed left upper lobe (Fig. 1). The bronchial tree itself is not sufficiently well outlined to show the point of bronchial occlusion. The heart is not appreciably increased in size, although the obscuration of the left margin makes accurate measurement impossible. The lungs are otherwise emphysematous, and there are a few linear streaks in the right-middle-lung region and at the base that may be due to atelectasis or scars.

Dr. Bird: If fluoroscopy was feasible, what did it show? I am particularly interested in motion of the left hemidiaphragm.

Dr. Hanelin: I am not personally acquainted with this case and am unable to tell you whether the diaphragm moved normally on the left side. Even in the last examination there is probably some residual fluid at the base, which makes it difficult accurately to determine the level of the diaphragm without the aid of air or barium in the stomach. There probably is, however, abnormal elevation of the left leaf of the diaphragm, and I suspect that paradoxical motion was present.

Dr. Bird: This review of the actual x-ray films of the chest with the roentgenologist is more helpful than the description in the protocol.

A so-called collapsed left upper lobe can result from chronic infection with fibrosis and reduction in volume or from a lobar occlusion. Despite the left-sided pleural effusion with its predominance of lymphocytes, I shall exclude tuberculosis and other chronic infections. Lobar obstruction due to pulmonary neoplasm is an attractive explanation. Such a tumor could easily reach the heart or pericardium

*Assistant in medicine, Massachusetts General Hospital.

either by direct extension or by invasion of the pulmonary veins and subsequent coronary-artery embolization. The patient was obviously too ill for bronchoscopy, which might have been diagnostic in this case. Cytologic examination of the pleural fluid could well have shown tumor cells, but the protocol was silent on this point.

The course in the hospital was marked by recurrent cardiac arrhythmias and increasing drowsiness. The latter could have been caused by an increasing derangement of serum electrolytes or, if oxygen therapy was continued, it is possible that so-called carbon dioxide narcosis with the development of coma ensued. The persistent elevation of the white-cell count could have been the result of neoplastic invasion of the bone marrow, since there was no particular evidence of a site of infection, other than within the contracted left upper lobe. The blood cultures were negative; sputum culture was not revealing, and the temperature rose to only 100°F. The variable cardiac arrhythmias became of increasing concern to the physicians. One can wonder about the role of digitalis intoxication in the production of these arrhythmias since the maintenance ration was supplemented by a parenteral preparation on several occasions. Despite the uremia, the stopping of digitalis and the cautious use of potassium chloride might have settled the point. Digitalis intoxication develops more easily in the presence of hypokalemia. Although I cannot exclude digitalis intoxication as a cause for at least some of the cardiac irregularities, these could also have been due to metastatic invasion of the heart, especially in the region of the right atrium. The pleuropericardial friction rub could, in turn, have been caused by metastases to the pericardium or by an actual recent myocardial infarction.

Neoplastic invasion of the pulmonary vascular system, even with multiple tumor emboli, is possible. Pulmonary hypertension with varying degrees of pulmonary disability results. But there are no clinical data to support this suggestion. Lymphangitic carcinomatosis could produce the increased markings in the right lung, but the absence of hilar adenopathy on the right argues against this possibility.

In summary, the single disease that would best explain the clinical and roentgenologic findings is a neoplasm, probably a bronchogenic carcinoma, originating in the left upper lobe, which was markedly reduced in size as a result of lobar occlusion. Secondary overdistention of the left lower lobe had resulted. In addition, I believe this patient had a myocardial infarction as a result of coronary occlusion, possibly from tumor emboli, with additional invasion of the heart and pericardium by neoplasm. The mediastinum and left pleural space were involved by the same process.

Clinical Diagnoses

Pulmonary emphysema and fibrosis.
Bronchial asthma.
? Bronchogenic carcinoma, left-upper-lobe bronchus.

Dr. Kenneth T. Bird's Diagnoses

Bronchogenic carcinoma, with invasion of heart and pericardium.
Myocardial infarction.

Anatomical Diagnoses

Squamous-cell carcinoma, lingular division of left upper lobe, with metastases to regional lymph nodes and direct extension into left atrium of heart.
Hydrothorax, left.
Fibrinous pericarditis.
Pulmonary emphysema.
Cor pulmonale, chronic.
Coronary sclerosis, severe.

Pathological Discussion

Dr. Leonard Atkins: Dr. Rabkin, will you tell us the opinion on the ward?

Dr. Mitchell T. Rabkin: Initially, we were impressed by the history of marked physical incapacity for many months. We thought that the diagnoses were chronic pulmonary disease and coronary-artery disease. With the findings of absent breath sounds over the left apex, the diagnosis of cancer of the lung was suggested. It was considered seriously after Dr. Gordon S. Myers pointed out that the arrhythmias were suggestive of pericardial or myocardial metastatic disease.

Dr. Atkins: At autopsy the left pleural cavity contained 1500 ml. of clear, straw-colored fluid. A hard, nodular mass of tumor that measured 3 cm. by 4 cm. by 4 cm. was found in the hilar region on the left. The tumor, which proved to be a squamous-cell carcinoma microscopically, apparently arose from the proximal portion of the inferior segmental bronchus of the lingular division of the left upper lobe. There was submucosal extension of tumor, with involvement of the left main bronchus and the carina, as well as extension into the left atrium by a fungating, necrotic mass of tumor that measured 3 cm. by 3 cm. by 2 cm. The tumor replaced the pulmonary veins on the left, which could not be identified. Metastases were found in the regional lymph nodes, but no distant metastases were found. Both lungs showed extensive emphysema.

The pericardial cavity contained 120 ml. of cloudy, yellow fluid with fibrinous adhesions. The heart weighed 370 gm., and, commensurate with long-standing pulmonary emphysema, there were dilatation and hypertrophy of the right ventricle, which measured 7 mm. in thickness. There was severe disease of the coronary arteries but no evidence of myocardial infarction. The liver was normal in size and showed slight central congestion. Except for finely granular cortical surfaces and several depressed scars the kidneys were unremarkable. There was severe atherosclerosis of the aorta and peripheral arteries.

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ANTIBIOTIC COMBINATIONS

THE opening remarks at the Fourth Annual Symposium on Antibiotics held recently in Washington called attention to the "distinct and dynamic trend toward combined antibiotics" and suggested that a new era in the antibiotics age may be beginning.[1] These remarks received considerable attention and publicity. However, although they only presented some data without analysis or criticism, the very fact that they were made by one with considerable prestige and authority in the field had the effect not only of acquiescence but even of dignifying and encouraging the trend and the direction into which it is being channeled.

The trend toward the production, sales and use of antibiotic combinations cannot be denied since it is being so energetically and aggressively pursued by some manufacturers and so often uncritically accepted by many physicians, who readily fall prey to the psychologic warfare embodied in the high-powered technics of modern sales promotion. However, it may be well to stop and consider the present status of the problems involved, the wisdom and implications of pursuing the trend and the manner in which it is being exploited. For, if this trend is permitted to continue to develop unfettered and unchallenged, the inevitable result will be a flood of the market with innumerable combinations, only a few of which might eventually prove to be acceptable — and an exceptional one perhaps even superior. Most of the combinations will inevitably consist of inferior and undesirable agents; some may combine useful agents unnecessarily, or useful ones with others that are either new and untried or old and inferior. (Witness the host of combinations containing gramicidin and tyrothricin, long since discarded as inferior agents.) In particular some manufacturers are inclined to incorporate products in which they have a proprietary interest (or at least in which their competitors have not) rather than products that are the best available but in which they do not have such interests.

To begin with, it is well to point out that the tendency of many physicians to prescribe combinations of antimicrobial agents and of manufacturers or dealers to supply them together in convenient formulations — such as tablets, capsules, suspensions and sterile vials — really began as soon as more than one effective agent was available. The trend was markedly accelerated after penicillin and streptomycin both became freely available. At present, all the major pharmaceutical companies are marketing some combinations of antimicrobial agents; some of them offer many such combinations in addition to mixtures of antibiotics with other unrelated agents, notably antihistamines, adrenocortical steroids and vitamins. Most often the only justification for including one or another of the components is the fact that it

is being produced by the particular manufacturer or that pressure is brought to bear on the management by the sales force to provide some combination to meet effective competition. A number of reasons are generally given to justify, or at least to rationalize, the use of the antibiotic combinations; it may therefore be of interest to reiterate and to discuss briefly some of the principal ones.

It is claimed that multiple agents when used together may broaden the spectrum of antibacterial activity. No good reason can be offered to indicate that this should be either necessary or desirable in most cases for which antibiotic combinations are actually used. By far the greatest majority of serious acute bacterial infections respond equally well to single effective agents when used properly.

Secondly, antibiotics in combination are deemed to be desirable because they may attack the bacteria by different modes of action — a sort of "crossfire" — and in this way, or possibly by other mechanisms, may exert "synergistic effects." Such a synergistic action has been demonstrated in specific circumstances in vitro and occasionally in experimental infections, but cases in which it has been demonstrated in the treatment of human disease are extremely rare and must be selected under careful bacteriologic control.[2,3] However, the possibility must also be considered that in any given case, or under certain circumstances, these different actions will have the opposite effect — that is, the mode of action of one agent may be such as to interfere with the operation of the other, and the net effect may be to neutralize or even to antagonize each other.

Thirdly, it is claimed that the use of multiple agents permits a reduction in the dose of each component and that this may result in a reduction in toxicity. There is little evidence that the usual reduction in dosage of any agent permitted by its use in combination with others does, in fact, diminish toxicity, except in rare and special cases — for example, when a proper dose of a combination of sulfadiazine with its methyl derivatives, sulfamerazine and sulfamethazine, is used to diminish crystalluria, or when streptomycin is used together with its hydrogenated derivative, dihydrostreptomycin, to reduce the amount and degree of eighth-nerve toxicity. The alternative possibilities must also be given equal consideration — namely, that an even larger total dose of the combination may be required for a comparable clinical effect in any given case and that toxic effects may result from each component of the combinations.

Fourthly, antibiotics in combinations are recommended to prevent the emergence of antibiotic-resistant strains, but this result can be achieved only within limits and with certain combinations, when these are properly and intelligently applied and then only in special circumstances. In actual practice, suppression of resistance has been clearly demonstrated only during the treatment of tuberculosis, and then only with certain combinations of dosages of streptomycin, para-aminosalicylic acid and isoniazid used in proper relations. The tendency of originally sensitive strains of many species to develop resistance to streptomycin, erythromycin and novobiocin individually in vitro may be reduced by the concomitant use of another effective agent; although this may be considered a proper use of such combinations there is no clear evidence that the desired effect has indeed been accomplished in the treatment of patients.[4]

In this connection it should be pointed out that the major problem during therapy with most antibiotics is not the development of resistance by originally sensitive strains but rather the overgrowth of originally resistant ones that are not affected by the therapy. This overgrowth is not avoided, but may actually be encouraged by the use of combined therapy. The resulting infections, when they occur, may be highly resistant to all antimicrobial agents.[4] It is also well to call attention here to the fact that three recently introduced antibiotics — namely, carbomycin (Magnamycin), oleandomycin (PA 105, Matromycin) and spiramycin (Rovomycine) — are all closely related in activity, and probably also in structure, to erythromycin. All these new agents are considerably less active, weight for weight, than erythromycin, and all exhibit complete crossresistance to one another after exposures of staphylococci to any one of them in vitro.[5] The relative effectiveness of oleandomycin or spiramycin in actual therapy as compared with erythromycin cannot yet be evaluated from available reports, but carbomycin has clearly been demonstrated to be inferior. Moreover, it was recently shown[6] that the routine administration of novobiocin and spiramycin in combination resulted in the appearance of strains of staphylococci resistant to one, or the other, or both of these antibiotics among hospital personnel when before such a use all or nearly all such staphylococci were sensitive to both agents. There was also an accompanying increase in the proportion of strains resistant to erythromycin.

Finally, it was pointed out that certain combinations of antimicrobial agents have already been clearly demonstrated to give superior clinical results when compared with their individual components used separately. Various combinations of streptomycin, para-aminosalicylic acid and isoniazid in tuberculosis, any one of the tetracyclines with streptomycin in brucellosis and penicillin with streptomycin in enterococcal endocarditis can be cited as examples. It should be emphasized, however, that these are the *only* examples of proper systemic use of combined antimicrobial agents. Even so, there are not available at present any formulations of any of the combinations mentioned in proper relations of the components so as to provide optimum or even acceptable therapy for any one of these diseases in which they have been shown to be useful. It may be mentioned,

parenthetically, that current evidence indicates the prolonged administration of one of the tetracyclines alone is the treatment of choice in brucellosis.[7]

Perhaps the most effective sales arguments advanced to convince physicians of the value to them of combined antibiotics in single packages are that they are convenient and that their use obviates the necessity of specific diagnosis. Such arguments are indeed deplorable, for, like the distorted, biased and misleading information and half-truths so often imparted by certain enthusiastic and energetic salesmen or by the literature of the less scrupulous among the manufacturers, they have the net effect of vitiating and negating the tremendous efforts now being expended in the noncommercial medical literature and in the countless programs of medical education, both predoctoral and postdoctoral. In fact, one of the most serious objections to the use of predetermined and packaged combinations of agents of any sort is that they tend to remove another incentive for the physician to acquire and to apply intelligently the knowledge essential for the proper management of his patients. Moreover, no package containing a predetermined combination of agents can offer the flexibility and individualization required to offer optimum therapy to any given patient.

What has been said applies particularly to combinations of agents for systemic use. Certain combinations of agents may have advantages in topical therapy, for here it may be possible to formulate combinations for specific purposes that may be expected more nearly to approximate in vitro effects, but these, again, must be carefully selected and must be demonstrated to have the desired effect in actual therapy. However, the possibilities of sensitization to each of the antimicrobial agents in the combination and the need for tailoring the antibiotics to the particular infecting bacteria are not obviated.

In the last analysis, the final test of whether combinations of agents have advantages over single ones must await the results of carefully documented and controlled clinical studies. These are becoming increasingly difficult to carry out, and may eventually require new technics and concerted efforts such as those demonstrated to be effective in tuberculosis therapy in the co-operative studies of the Veterans Administration in this country and of the Medical Research Council in Great Britain.

Meanwhile, any carefully controlled studies that will bring together useful comparisons of individual and combined agents in human beings should be helpful as a preliminary screening procedure. The antibacterial action of the blood of persons receiving such agents may be one such procedure.

Elsewhere in this issue of the *Journal* the results of a study of one antibiotic combination — namely, that of erythromycin and penicillin — that there had been some reason to believe might be antagonistic[8] are reported. Actually, however, previous studies in the same laboratory, not cited in the present paper, had shown at least an additive effect and a definite delay and decrease in rate of emergence of resistance from the same combination in vitro.[9] The studies reported here indicate that, when put in a single capsule, the combination could indeed be antagonistic. The antibacterial action of the plasma of persons who had ingested such capsules was decidedly less than when the same amounts of the individual agents were ingested separately by the same persons. In this instance, however, it became evident that the apparently antagonistic effect was due to the particular formulation, for with other formulations the same pair of antibiotics had a purely additive effect, each component contributing only its share.

The authors of this paper have pursued this approach farther. In another paper, to be published in a later issue, data are presented to indicate similar results with a number of combinations, in pairs, of penicillins V and G, tetracycline and oleandomycin. In every case one member of the pair produced antibacterial activity in the plasma that was superior to that of the other, and the administration of the two in combination gave intermediate values both for the peak concentrations and for the total antibacterial activity achieved.

Although such findings cannot be said to tell the whole story and by themselves do not necessarily support or invalidate claims for superiority or inferiority of antibiotic combinations, they certainly suggest that such combinations, particularly when presented in a single package, should be approached with the greatest caution and skepticism. For, as every tradesman knows, "package deals" are generally offered by a seller primarily to boost the sales of unmarketable or poorly accepted products. Physicians should be particularly careful in accepting drugs purely on the basis of the manufacturer's evidence or on the basis of testimonials provided to the manufacturer. They should demand clear, unbiased, well studied and adequately controlled evidence produced and interpreted by reliable observers.

Caveat emptor!

References

1. Welch, H. Opening remarks. In *Antibiotics Annual 1956-1957* (in press).
2. Jawetz, E., and Gunnison, J. B. Antibiotic synergism and antagonism: assessment of problem. *Pharmacol. Rev.* **5**:175-192, 1953.
3. Jawetz, E. Antimicrobial therapy. *Ann. Rev. Microbiol.* **10**:85-114, 1956.
4. Finland, M. Emergence of antibiotic-resistant bacteria. *New Eng. J. Med.* **253**:909-922, 969-979 and 1019-1028, 1955.
5. Jones, W. R., Jr., and Finland, M. Resistance and cross-resistance *in vitro* to erythromycin, carbomycin, oleandomycin, spiramycin and streptogramin. *Proc. Soc. Exper. Biol. & Med.* **93**:(Nov., 1956).
6. Lepper, M. H., et al. Effect of routine use of novobiocin and spiramycin in combination on antibiotic sensitivity of hospital staphylococci. In *Antibiotics Annual, 1956-1957* (in press).
7. Spink, W. W. *The Nature of Brucellosis*. 464 pp. Minneapolis: University of Minnesota Press, 1956. P. 258.
8. Coleman, V. R., Gunnison, J. B., and Jawetz, E. Participation of erythromycin and carbomycin in combined antibiotic action *in vitro*. *Proc. Soc. Exper. Biol. & Med.* **83**:668-670, 1953.
9. Purcell, E. M., Wright, S. S., and Finland, M. Antibiotic combinations and resistance to antibiotics: penicillin-erythromycin and streptomycin-erythromycin combinations *in vitro*. *Proc. Soc. Exper. Biol. & Med.* **82**:124-131, 1953.

"SCIENCE AND FREEDOM"

TRUTH, of which science is a perpetual exponent, is always struggling to be free, and nowhere, according to a group of American physicists who visited that contradictory country last spring, is the aphorism more abundantly demonstrated than in modern Russia. The impressive advances observed by these visitors were described in the Baltimore *Sun* in June by Freeman Dyson, of the Institute for Advanced Study at Princeton, in an article that was later reprinted in *Science*.*

The question has been raised whether intellectual freedom can flourish and truth of any nature triumph in an atmosphere of political serfdom, and the answer seems to be that freedom is relative and specific, capable of being grooved and channeled, so fluid that it can run into the courses open to it even while it is blocked in other directions. This, in fact, was the state in Germany for many decades in the last century and early in the present one, when leadership in medicine and an appreciation of the arts were apparently compatible with virtual totalitarianism in government.

Russia, however, never a country distinguished for its technical progress, was submerged, so far as science is concerned, under the Soviet despotism that seemed such a short time ago to have reached its zenith in the rule of Stalin. For under the shadow of the Kremlin in his day no worker in a physics laboratory in Moscow was even permitted to know what was going on in any other center of research, and in certain of the sciences, as is well known, truth was hammered into the form that was decreed by authority. Before the war, in fact, "almost every piece of equipment more complicated than a screwdriver was imported" and "those gadgets which were made in Russia were not expected to function." Today the Russians, with an unprecedented two-year acceleration since the death of Stalin, are making scientific equipment as good as any in the world, and their achievements in physics, although not yet on a level with those in America, are nevertheless impressive considering the distance they have traveled in so short a time.

The important point is that the present Russian government, despite its ideologic obsessions and the multiple restrictions that it still imposes, is spending great sums on pure science and is determined to make Moscow the scientific capital of the universe. This, the rulers realize, can be achieved, if at all, only by a receptive attitude to new ideas and by attracting talent from the wide world.

Whereas Stalin closed Russia to that world, which he sought to undermine and acquire hegemony over, the new masters in the Kremlin, — still under the spell of the same dream of empire, — are presenting a more complicated type of opposition to the freedom of the west by competing with it in its own multiple fields of endeavor. Such competition must be taken seriously, but it need not all necessarily be viewed as sinister, and indeed a genuine search for basic truths can scarcely be conducted on a purely selfish level. For as competition is fundamentally healthy so it can also be friendly and reciprocal, and the promotion of any culture that requires intellectual freedom must thereby clear to some extent the fogs of misunderstanding and of mutual suspicion, at least at certain levels. This does not mean, unfortunately, that science and even a sort of culture cannot be linked with aggression, and already the new leaders have revealed the same insolence, the same viciousness and the same sadistic obsessions that characterized the old master.

*Dyson, F. Science and freedom. *Science* **124**:432, 1956.

THE DOCTOR'S MAIL

THE *Journal*, some months ago, commented editorially on an analysis that had been released from commercial sources relative to the amount of direct mail advertising received by physicians. Not only did the quantity of paper thus distributed suggest an appalling importunacy; a real problem of serious dimensions was believed to be presented by the unsolicited drug samples directed also at the hard-pressed practitioner. The Post Office itself raised an alarm regarding the latter, pointing out the danger involved in the indiscriminate discarding of undesired drug samples in waste receptacles that are often picked over by children and more professional scavengers.

A more recent survey has been published by a mailing firm specializing in addressing to the professions, comparing the quantity of mail received by a typical physician in a recent twelve-month period with that of similar periods ending in 1955, 1954 and 1953. According to this study, encouraging from the point of view of direct-mail-advertising agencies, possibly their clients, and certainly the printing and paper trades, the typical busy general practitioner received this year nearly 500 *more* mailings than in the preceding twelve-month period, bringing the heart-rending total to nearly 4500. Obviously, the agency admits, he does not have time to read all this mail and sometimes when he is particularly busy or unduly harassed he may not look at any of it. The answer to this, however, is simple. Lay it on. Repeat and repeat in the sanguine (or sanguinary) belief, cherished by all advertisers, that eventually he will break down and take one furtive look at the material with which he is being snowed under.

Of the total advertising mail received by the typical busy general practitioner who lent himself to the study, 90 per cent was from pharmaceutical houses, 2 per cent consisted of solicitations for medical books and journal subscriptions, 1 per cent was for medical equipment and instruments and 7 per cent was miscellaneous, including all mail of a nonmedical nature. Of minor encouragement is the notation that un-

solicited sampling is down for the second year in a row, a trend that may be balanced by the appearance of blotters in only 2.5 per cent of mailings, compared with their incidence of 14.6 per cent in 1948.

Among other statistics of greater or less importance certain changes in product classification are of interest. Thus, antiarthritics have bounded from 3.7 per cent of the pharmaceutical mail total in 1955 to 7.7 per cent in 1956. The antibiotics have returned to first place at 8.2 per cent, although this represents a drop from their second-place standing of 1955 with 9.9 per cent; cardiovascular drugs led in 1955 with 11 per cent and are this year in third place with 6.8 per cent.

Antidiarrheals, 1 per cent of the total, have made their first appearance, bearing perhaps some triangular relation to laxatives, which have gone up from 1.9 to 2.7 per cent, and hemorrhoidals, which have dropped from 1.4 to 0.8 per cent. Ataractics, the tranquilizers of yesteryear, have made their first appearance at 4.4 per cent and vaginal medication has risen from 1.2 per cent in 1954 and 2.1 in 1955 to 2.9 per cent in 1956.

Perhaps somewhere in all this obsessive play of the market place can be found a reflection or two on the ways that medicine must take in the fulfillment of its destiny.

OF MEN AND ARTHROPODS

THE war between man and the arthropods has been a continuous struggle since the former belatedly assumed his somewhat precarious place on the planet, and the end is not in sight nor the outcome assured. It is possible to imagine insect life as finally triumphant with the loss of a few species that require a human host, but the total extermination of arthropodal life would pose a serious problem for those who depend on crossfertilization for the germination of their crops, the consumption of crustaceans for the success of their shore dinners, insect colonization as examples of co-operative industry and the slapping of mosquitoes as a form of involuntary exercise.

Nevertheless, it is readily admitted that the numbers if not the varieties of flying, jumping, creeping and crawling creatures exceed by many trillions those for whom any purpose useful to man is clearly evident, and man could do very nicely without many of those that are the vectors of disease, that destroy the crops they have not helped to fertilize and that carry loaded weapons at one end or the other — that hurt when they appear to incline the head or seem to seat themselves on the surface of the human frame.

Human ingenuity in producing new weapons for the chemical warfare that has turned out to be so much more effective against the jointed invertebrates than crushing them between two shingles, one by one, has succeeded in keeping the warmer-blooded antagonist in the ascendancy, but barely so. The insects are protean in their morphology, diabolical in their adaptability and ultraresourceful in their ability to disappear, like earwigs (a European importation) until the coast is clear. Lest international relations suffer it may be stated that the importation of the earwig, the Dutch elm disease, the Japanese beetle, the English sparrow and the Arabian dromedary that once loped across the arid plains of Arizona has been said to be nothing compared to the effectiveness with which the American soldier seeded the receptive soil of France with *Epidermophyton floccosum* in 1918.

From the point of view of health problems alone, entirely unrelated to the finding of worms, or half-worms in apples, the World Health Organization has from its beginning interested itself in the control of such insect-borne diseases as malaria, yellow fever, typhus, plague, filariasis, kala-azar and the dysenteries. In these endemic and epidemic disorders that are carried by mosquitoes, various flies, fleas and lice, great progress in control has been made with the modern insecticides. Experience has shown, however, that insects can build up a resistance to these formulas even as bacteria, by the process of selection, perhaps, become resistant to the antibiotics, and man himself has gradually developed a degree of insusceptibility to a number of the living organisms or toxic substances that have threatened his existence.

In respect to the control of insect-borne disease, the World Health Organization, like the sun dial, warns its public that it is later than one thinks. Already insect resistance to the insecticides has appeared, and eradication programs, like those against malaria, must be accelerated before the time runs out. The situation suggests, but does not parallel, that of the driver who speeds on his way in the hope that an increase in velocity will bring him to his destination before his gasoline is exhausted. Meanwhile the search for new and better insecticides goes on.

Dr. Kane's Health. — *We regret to learn, through the public journals, that Dr. Kane, the celebrated voyager, is in such a delicate state of health, as to render it necessary for him to abandon his home and studies and to seek in a European tour to regain his lost bodily energy.* — St. Louis Medical and Surgical Journal.

Boston M. & S. J. *December 4, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

AORTIC AND MITRAL INSUFFICIENCY AND STENOSIS, PULMONARY EDEMA AND BRONCHOPNEUMONIA

A twenty-one-year-old gravida II, para I, was first seen at the twenty-second week of pregnancy. She gave a history of rheumatic fever in childhood but denied previous and present symptoms of congestive heart failure. Two years earlier pregnancy in another

city had produced a living infant, which had died of pneumonia at six weeks of age. It was subsequently learned that congestive heart failure had accompanied the end of that pregnancy and that the patient had been hospitalized for failure a year before when not pregnant. She did not admit all this, apparently fearing that interruption of pregnancy would be imposed. She denied dyspnea, orthopnea, hemoptysis and other cardiac symptoms at each of her weekly clinic visits. The blood pressure was 130 systolic, 0 diastolic. The heart had Grade 4 systolic and diastolic murmurs at the aortic area, a Grade 3 apical diastolic murmur and a Grade 4 apical systolic murmur. The lungs were clear at all times, and the vital capacity was about 1600 ml. Asymptomatic and with unchanged physical findings at thirty-six weeks she grudgingly consented to enter the hospital for a "cold". She had become anorectic, nauseated and febrile (temperature of 101°F.). Orthopnea requiring two pillows for relief developed during the night before admission, and dyspnea became severe.

On admission the temperature was 102°F., with dullness at the right-lung base, and the pulse 148. The heart size (enlarged to the left anterior axillary line) and murmurs were essentially unchanged.

Despite penicillin and streptomycin rales appeared at the lung bases posteriorly. On Digoxin intramuscularly and oxygen intranasally she improved symptomatically, and the lungs cleared. Shortly afterward, however, the pulse rose from 100 to 180, and she became dyspneic and cyanotic. An electrocardiogram showed atrial flutter. Morphine, digitalis and positive-pressure oxygen, as well as tourniquets, were used, but gross pulmonary edema developed, and the fetal heart became inaudible. The patient's condition improved for a short time and then she suddenly stiffened and cardiac sounds could no longer be heard.

Autopsy revealed rheumatic heart disease with insufficiency and stenosis of the aortic and mitral valves, pulmonary edema with bronchopneumonia and microscopic abscesses in the myocardium, presumably a result of the respiratory disease.

This was classified as a nonpreventable death with reservations. If one accepts the philosophy that physicians may accept responsibility only for the immediate situation, there was indeed nothing in the patient's management or care that warrants criticism or comment. The downhill course was sufficiently inexorable to provide a graphic exception to what has recently been considered almost the rule among pregnant cardiac patients — namely, that with sufficient bed rest and proper attention any cardiac patient can be safely brought through pregnancy. This contradiction of that widely held opinion is thus perhaps valuable, for it illustrates the seriousness of adding even the trivial burden of coryza to a diseased heart in pregnancy. Clinical estimates of the heart's capacity to stand this extra strain are not accurate.

Assuming on the other hand, however, that the patient had not deliberately avoided medical care, and assuming that she could have had the pregnancy interrupted during the first trimester, there seems no question that she would now be alive. The case would then have to be called a preventable death, with responsibility assigned to the patient herself. Lending weight to this indictment of responsibility is the fact that she deliberately falsified the history, deliberately avoided medical care, fearing an interruption, and later accepted hospitalization only grudgingly. Perhaps organized medicine as a whole should assume some responsibility for not having convinced her of the gravity of this situation and of the importance of following advice.

JOHN FIGGIS JEWETT, M.D.
Chairman

NOTICES

MASSACHUSETTS HEART ASSOCIATION

The kidney section of the Massachusetts Heart Association will hold a meeting at the Morse Auditorium, Museum of Science, Science Park, Boston, on Monday, December 10, at 8 p.m.

Dr. John Eager Howard will talk on "Unilateral Kidney Disease and Hypertension." Physicians and medical students are invited.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, DECEMBER 6

THURSDAY, DECEMBER 6

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
8:00–9:00 a.m. Medical Journal Club. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00 a.m. Neurological Rounds. Dr. Kane. Evans 2 Conference Room, Massachusetts Memorial Hospitals.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*10:15 a.m.–12:00 m. Medical Grand Rounds. Dr. Keefer. Evans 8 Amphitheater, Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Some New Ways to Assess the Coronary Circulation of Man. Dr. Richard Gorlin. Main Amphitheater, Peter Bent Brigham Hospital.
*3:30 p.m. Gastroenterology Conference. Dr. Ingelfinger. Massachusetts Memorial Hospitals.

FRIDAY, DECEMBER 7

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*11:30 a.m. Tumor Clinic. Drs. Soutter and Lemon. Robinson 4, Massachusetts Memorial Hospitals.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

(Concluded on page xxxv)